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Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults (Review)

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[Diagnostic Test Accuracy Review]

Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

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ABSTRACT

Background

Accurate, rapid detection of tuberculosis (TB) and TB drug resistance is critical for improving patient care and decreasing TB transmission. Xpert® MTB/RIF assay is an automated test that can detect both TB and rifampicin resistance, generally within two hours after starting the test, with minimal hands-on technical time. The World Health Organization (WHO) issued initial recommendations on Xpert® MTB/RIF in early 2011. A Cochrane Review on the diagnostic accuracy of Xpert® MTB/RIF for pulmonary TB and rifampicin resistance was published January 2013. We performed this updated Cochrane Review as part of a WHO process to develop updated guidelines on the use of the test.

Objectives

To assess the diagnostic accuracy of Xpert® MTB/RIF for pulmonary TB (TB detection), where Xpert® MTB/RIF was used as both an initial test replacing microscopy and an add-on test following a negative smear microscopy result.

To assess the diagnostic accuracy of Xpert® MTB/RIF for rifampicin resistance detection, where Xpert® MTB/RIF was used as the initial test replacing culture-based drug susceptibility testing (DST).

The populations of interest were adults presumed to have pulmonary, rifampicin-resistant or multidrug-resistant TB (MDR-TB), with or without HIV infection. The settings of interest were intermediate- and peripheral-level laboratories. The latter may be associated with primary health care facilities.

Search methods

We searched for publications in any language up to 7 February 2013 in the following databases: Cochrane Infectious Diseases Group Specialized Register; MEDLINE; EMBASE; ISI Web of Knowledge; MEDION; LILACS; BIOSIS; and SCOPUS. We also searched the metaRegister of Controlled Trials (mRCT) and the search portal of the WHO International Clinical Trials Registry Platform to identify ongoing trials.

Selection criteria

We included randomized controlled trials, cross-sectional studies, and cohort studies using respiratory specimens that allowed for extraction of data evaluating Xpert® MTB/RIF against the reference standard. We excluded gastric fluid specimens. The reference standard for TB was culture and for rifampicin resistance was phenotypic culture-based DST.

Data collection and analysis

For each study, two review authors independently extracted data using a standardized form. When possible, we extracted data for subgroups by smear and HIV status. We assessed the quality of studies using QUADAS-2 and carried out meta-analyses to estimate pooled sensitivity and specificity of Xpert® MTB/RIF separately for TB detection and rifampicin resistance detection. For TB detection, we performed the majority of analyses using a bivariate random-effects model and compared the sensitivity of Xpert® MTB/RIF and smear microscopy against culture as reference standard. For rifampicin resistance detection, we undertook univariate meta-analyses for sensitivity and specificity separately to include studies in which no rifampicin resistance was detected.

Main results

We included 27 unique studies (integrating nine new studies) involving 9557 participants. Sixteen studies (59%) were performed in low- or middle-income countries. For all QUADAS-2 domains, most studies were at low risk of bias and low concern regarding applicability.

As an initial test replacing smear microscopy, Xpert® MTB/RIF pooled sensitivity was 89% [95% Credible Interval (CrI) 85% to 92%] and pooled specificity 99% (95% CrI 98% to 99%), (22 studies, 8998 participants: 2953 confirmed TB, 6045 non-TB).

As an add-on test following a negative smear microscopy result, Xpert®MTB/RIF pooled sensitivity was 67% (95% CrI 60% to 74%) and pooled specificity 99% (95% CrI 98% to 99%; 21 studies, 6950 participants).

For smear-positive, culture-positive TB, Xpert® MTB/RIF pooled sensitivity was 98% (95% CrI 97% to 99%; 21 studies, 1936 participants).

For people with HIV infection, Xpert® MTB/RIF pooled sensitivity was 79% (95% CrI 70% to 86%; seven studies, 1789 participants), and for people without HIV infection, it was 86% (95% CrI 76% to 92%; seven studies, 1470 participants).

Among 180 specimens with nontuberculous mycobacteria (NTM), Xpert® MTB/RIF was positive in only one specimen that grew NTM (14 studies, 2626 participants).

Comparison with smear microscopy

In comparison with smear microscopy, Xpert® MTB/RIF increased TB detection among culture-confirmed cases by 23% (95% CrI 15% to 32%; 21 studies, 8880 participants).

For TB detection, if pooled sensitivity estimates for Xpert® MTB/RIF and smear microscopy are applied to a hypothetical cohort of 1000 patients where 10% of those with symptoms have TB, Xpert® MTB/RIF will diagnose 88 cases and miss 12 cases, whereas sputum microscopy will diagnose 65 cases and miss 35 cases.

Rifampicin resistance

For rifampicin resistance detection, Xpert® MTB/RIF pooled sensitivity was 95% (95% CrI 90% to 97%; 17 studies, 555 rifampicin resistance positives) and pooled specificity was 98% (95% CrI 97% to 99%; 24 studies, 2411 rifampicin resistance negatives).

For rifampicin resistance detection, if the pooled accuracy estimates for Xpert® MTB/RIF are applied to a hypothetical cohort of 1000 individuals where 15% of those with symptoms are rifampicin resistant, Xpert® MTB/RIF would correctly identify 143 individuals as rifampicin resistant and miss eight cases, and correctly identify 833 individuals as rifampicin susceptible and misclassify 17 individuals as resistant. Where 5% of those with symptoms are rifampicin resistant, Xpert® MTB/RIF would correctly identify 48 individuals as rifampicin resistant and miss three cases and correctly identify 931 individuals as rifampicin susceptible and misclassify 19 individuals as resistant.

Authors' conclusions

In adults thought to have TB, with or without HIV infection, Xpert® MTB/RIF is sensitive and specific. Compared with smear microscopy, Xpert® MTB/RIF substantially increases TB detection among culture-confirmed cases. Xpert® MTB/RIF has higher sensitivity for TB detection in smear-positive than smear-negative patients. Nonetheless, this test may be valuable as an add-on test

following smear microscopy in patients previously found to be smear-negative. For rifampicin resistance detection, Xpert® MTB/RIF provides accurate results and can allow rapid initiation of MDR-TB treatment, pending results from conventional culture and DST. The tests are expensive, so current research evaluating the use of Xpert® MTB/RIF in TB programmes in high TB burden settings will help evaluate how this investment may help start treatment promptly and improve outcomes.

PLAIN LANGUAGE SUMMARY

Xpert MTB/RIF test for diagnosing pulmonary tuberculosis and rifampicin resistance in adults

Tuberculosis (TB) causes tremendous suffering worldwide, especially in low-income and middle-income countries. In 2012, 8.6 million people developed TB disease (active TB) for the first time and around 1.3 million people died. Most people with TB can be cured if the disease is diagnosed and properly treated. One of the problems in treating TB is that the bacteria become resistant to antibiotics. Detecting TB and TB drug resistance quickly is important for improving health, reducing deaths, and decreasing the spread of TB in communities.

Xpert® MTB/RIF is a new test that quickly detects TB and rifampicin resistance at the same time. Rifampicin is an important drug for treating people with TB. Since the test is automated, it does not require expert staff or an advanced laboratory.

Our objectives were to determine the diagnostic accuracy (sensitivity and specificity) for TB detection and rifampicin resistance detection. Sensitivity shows how often the test gives a positive result in people who really have TB. Specificity shows how often the test gives a negative result in people who do not have TB.

We included studies of adults with or without HIV infection thought to have pulmonary TB (TB in the lungs) or rifampicin resistance, and were most interested in the use of Xpert® MTB/RIF outside of the most advanced laboratories.

We also compared the sensitivity of Xpert® MTB/RIF to that of smear microscopy, the test commonly used for TB diagnosis in low- and middle-income countries. Smear microscopy is low-cost and fairly easy to do, but requires trained staff and is a hassle for patients, who must provide at least two sputum samples. Also, microscopy gives no information about drug resistance.

We searched for publications in any language up to 7 February 2013 and considered the study's risk of giving biased results.

What the results say

We included 27 studies involving around 9500 people. Most studies were performed in low- or middle-income countries. We thought most studies had a low risk of bias.

The key findings were:

For TB detection, Xpert® MTB/RIF was accurate (it was highly sensitive (89%), detecting almost all cases; and specific (99%), that is, not registering positive in people who were actually negative).

For rifampicin resistance detection, Xpert® MTB/RIF was accurate that is sensitive (95%) and specific (98%).

Xpert® MTB/RIF appeared to have similar accuracy in people with and without HIV infection.

Applying the findings of the review to an imaginary group of 1000 people who go to their doctor with symptoms, but where only 100 of them (10%) actually have TB, Xpert® MTB/RIF would diagnose 88 cases and miss 12 cases, whereas smear microscopy would diagnose 65 cases and miss 35 cases.

To summarize, our review shows that Xpert® MTB/RIF is more accurate than smear microscopy for diagnosing TB and also accurate for detecting rifampicin resistance. Xpert® MTB/RIF may be useful in many countries, as it does not require advanced laboratory facilities or expert staff.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Review question: What is the diagnostic accuracy of Xpert MTB/RIF assay for detection of pulmonary TB?
Patients/population: Adults with presumed pulmonary TB
Role: Xpert MTB/RIF assay used as an initial test replacing microscopy and used as an add-on test following a negative smear microscopy result
Index test: Xpert MTB/RIF assay
Reference standards: Solid or liquid culture
Studies: Cross-sectional
Setting: Mainly intermediate level laboratories

Type of analysis	Effect (95% credible interval)	No. of participants (studies)	Test result	Number of results per 1000 patients tested (95% CrI)[1]		
				Prevalence 2.5%	Prevalence 5%	Prevalence 10%
TB detection, Xpert MTB/RIF used as an initial test replacing smear microscopy	Median pooled sensitivity 89% (85, 92) and median pooled specificity 99% (98, 99)	8998 (22)	True Positives False Negatives False Positives True Negatives	22 (21, 23) 3 (2, 4) 10 (10, 20) 965 (956, 965)	45 (43, 46) 6 (4, 8) 10 (10,19) 941 (931, 941)	89 (85, 92) 11 (8, 15) 9 (9, 18) 891 (882, 891)
Smear-positive, culture-positive	Median pooled sensitivity 98% (97, 99); specificity of Xpert MTB/RIF could not be estimated in these studies	1936 (21)	True Positives False Negatives False Positives True Negatives	25 (24, 25) 1 (0, 1) *** ***	49 (49, 50) 1 (1, 2) *** ***	98 (97, 98) 2 (1, 3) *** ***
Smear-negative, culture-positive	Median pooled sensitivity 67% (60, 74) and median pooled specificity 99% (98, 99)	7565 (21)	True Positives False Negatives False Positives True Negatives	17 (15, 19) 8 (7, 10) 10 (10, 20) 965 (956, 965)	34 (31, 37) 16 (13, 20) 10 (10, 19) 941 (931, 941)	68 (61, 74) 32 (26, 39) 9 (9, 18) 891 (882, 891)
HIV-positive	Median pooled sensitivity 79% (70, 86) and median pooled specificity 98% (96, 99)	1789 (7)	True Positives False Negatives False Positives True Negatives	20 (18, 22) 5 (4, 8) 20 (10, 39) 956 (936, 965)	40 (35, 43) 11 (7,15) 19 (10,38) 931 (912, 941)	79 (70, 86) 21 (14, 30) 18 (9, 36) 882 (864, 891)

HIV-negative	Median pooled sensitivity 86% (76, 92) and median pooled specificity 99% (98, 100)	1470 (7)	True Positives False Negatives False Positives True Negatives	22 (19, 23) 4 (2, 6) 10 (10, 20) 965 (956, 965)	43 (38, 46) 7 (4,12) 10 (10,19) 941 (931, 941)	86 (76, 92) 14 (8, 24) 9 (9, 18) 891 (882, 891)
TB detection, Xpert MTB/RIF used as an add-on test following a negative smear microscopy result	Median pooled sensitivity 67% (60, 74) and median pooled specificity 99% (98, 99)	7151 (23)	True Positives False Negatives False Positives True Negatives	17 (15, 19) 8 (7, 10) 10 (10, 20) 965 (956, 965)	34 (30, 37) 17 (13, 20) 10 (10,19) 941 (931, 941)	67 (60, 74) 33 (26, 40) 9 (9, 18) 891 (882, 891)

1. The WHO suggested prevalence levels.

BACKGROUND

Tuberculosis (TB) is one of the world's most important infectious causes of morbidity and mortality among adults. When TB is detected and effectively treated, the disease is largely curable. However, in 2012, 8.6 million people developed TB disease (active TB) for the first time (WHO Global Report 2013). Of the 8.6 million TB cases, 1.1 million, approximately 13%, occurred among people with HIV infection. In 2012, 1.3 million people died of TB, including 320,000 deaths (25%) among people who were HIV positive (WHO Global Report 2013).

Drug-resistant TB, including multidrug-resistant TB (MDR-TB, defined as resistance to at least isoniazid and rifampicin, the two most important first-line anti-TB drugs) and extensively drug-resistant TB (XDR-TB, defined as MDR-TB plus resistance to any fluoroquinolone, such as ofloxacin or moxifloxacin, and to at least one of three injectable second-line drugs, amikacin, capreomycin, or kanamycin) has emerged as a serious threat to global health (Zumla 2012). In 2012, around 450,000 people developed MDR-TB and an estimated 170,000 died from MDR-TB (WHO Global Report 2013). Recently, the World Health Organization (WHO) reported the highest rates of MDR-TB (greater than 65% in people who had previously received TB treatment) ever recorded in several areas of the former Soviet Union (Zignol 2012). Worldwide, for all forms of TB, a substantial percentage (~35%) of patients are undiagnosed and a staggering percentage (~75%) of patients with MDR-TB remain undiagnosed (WHO Global Report 2013). Under 3% of people diagnosed with TB are tested to determine the pattern of drug resistance (Chaisson 2012). In addition to drug resistance, another major challenge is the accurate detection of smear-negative disease, which disproportionately occurs in HIV-positive people with TB (Harries 2004).

Accurate and rapid detection of TB, including smear-negative TB and drug resistant-TB, is critical for improving patient outcomes (increased cure and decreased mortality, additional drug resistance, treatment failure, and relapse) and decreasing TB transmission. Mycobacterial culture is generally considered the best available reference standard for TB diagnosis and is the first step in detecting drug resistance. However, culture is a relatively complex and slow procedure. Solid culture typically takes between four to eight weeks for results and liquid culture, though more rapid than solid culture, requires days and is more prone to contamination (WHO Policy Framework 2010). In addition, culture requires specialized laboratories and highly skilled staff. In early 2011, WHO endorsed a novel, rapid, automated, cartridge-based nucleic acid amplification test (NAAT), the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, USA) (hereafter referred to as Xpert MTB/RIF), that can simultaneously detect TB and rifampicin resistance (WHO Policy Xpert MTB/RIF 2011).

Target condition being diagnosed

Tuberculosis

TB is caused by the bacterium *Mycobacterium tuberculosis* and is spread from person to person through the air. TB most commonly affects the lungs (pulmonary TB), but may affect any organ or tissue, such as the brain or bones, outside of the lungs (extrapulmonary TB). Signs and symptoms of pulmonary TB include cough for at least two weeks, fever, chills, night sweats, weight loss, haemoptysis (coughing up blood), and fatigue. Signs and symptoms of extrapulmonary TB depend on the site of disease. TB treatment regimens must contain multiple drugs to which the organisms are sensitive to be effective. The treatment of MDR-TB is complex, usually requiring two years or more of therapy and drugs that are less potent and more toxic than the drugs used to treat drug-susceptible TB. The WHO issues international guidelines for TB treatment which are regularly updated.

Rifampicin resistance

Rifampicin inhibits bacterial DNA-dependent RNA polymerase, encoded by the RNA polymerase gene (*rpoB*) (Hartmann 1967). Resistance to this drug has mainly been associated with mutations in a limited region of the *rpoB* gene (Telenti 1993). Rifampicin resistance may occur alone or in association with resistance to isoniazid and other drugs. In high MDR-TB settings, the presence of rifampicin resistance alone may serve as a proxy for MDR-TB (WHO Rapid Implementation 2011). Patients with drug-resistant TB can transmit the infection to others.

Index test(s)

Xpert MTB/RIF is an automated polymerase chain reaction (PCR) test (molecular test) utilizing the GeneXpert® platform (Blakemore 2010Blakemore 2010; Cepheid 2009; Helb 2010). Xpert MTB/RIF is a single test that can detect both *M. tuberculosis* complex and rifampicin resistance within two hours after starting the test, with minimal hands-on technical time. Unlike conventional nucleic acid amplification tests (NAATs), Xpert MTB/RIF is unique because sample processing and PCR amplification and detection are integrated into a single self-enclosed test unit, the GeneXpert cartridge. Following sample loading, all steps in the assay are completely automated and self-contained. In addition, the assay's sample reagent, used to liquefy sputum, has potent tuberculocidal (the ability to kill TB bacteria) properties and so largely eliminates biosafety concerns during the test procedure (Banada 2010Banada 2010). These features allow the technology to be taken out of a reference laboratory and used nearer to the patient (Small 2011). Xpert MTB/RIF requires an uninterrupted and stable electrical power supply, temperature control, and yearly cali-

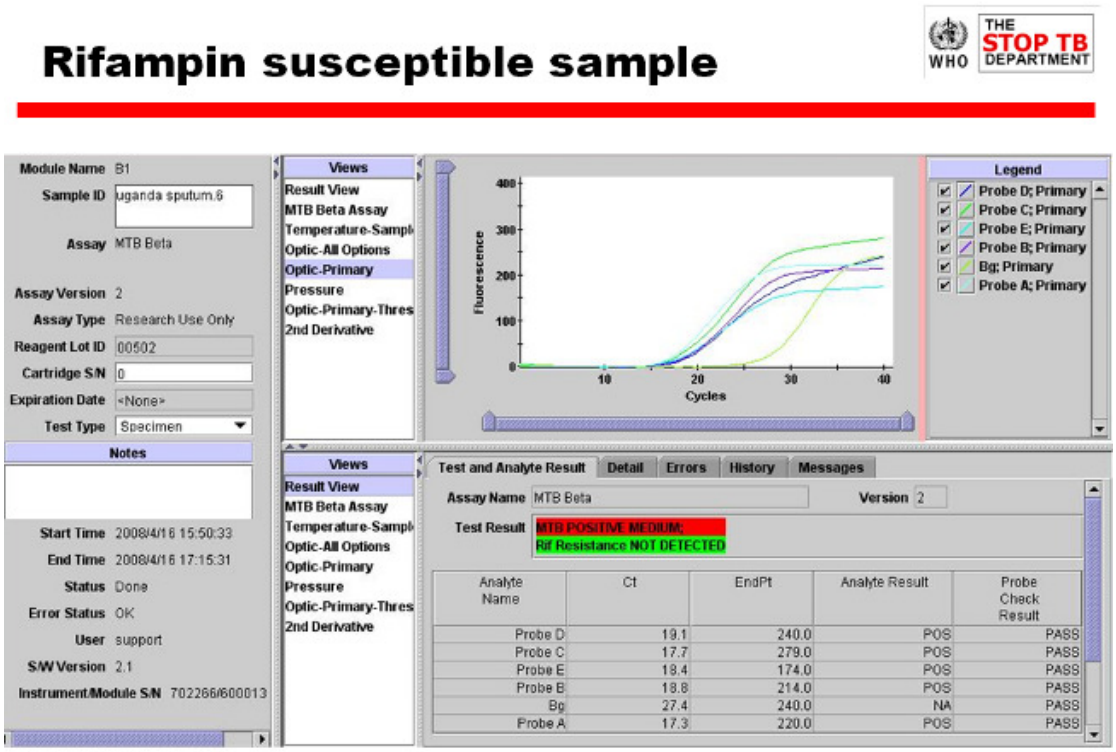
bration of the cartridge modules (WHO Rapid Implementation 2011).

The test procedure may be used directly on clinical specimens, either raw sputum samples or sputum pellets (also called sputum sediment) created after decontaminating and concentrating the sputum (Blakemore 2010). In both cases, the test material is combined with the assay sample reagent, mixed by hand or vortex, and incubated at room temperature for 15 minutes. After the incubation step, 2 mL of the treated sample are transferred to the cartridge and the run is initiated (Helb 2010). According to the manufacturer, Xpert MTB/RIF may be used with fresh sputum samples, which may be either unprocessed sputum or processed sputum sediments. The sample reagent (sodium hydroxide and isopropanol):sample volume ratio is 2:1 for unprocessed sputum and 3:1 for sputum sediments. The manufacturer does not specifically mention the use of Xpert MTB/RIF with frozen specimens (Cepheid 2009).

The Xpert MTB/RIF limit of detection, "the lowest number of colony forming units per sample that can be reproducibly distinguished from negative samples with 95% confidence" (Cepheid 2009), is five genome copies of purified DNA per reaction or 131 colony forming units per mL in *M. tuberculosis* spiked sputum (Helb 2010). In comparison, identification of TB bacilli by microscopic examination requires at least 10,000 bacilli per mL of sputum (Toman 2004). Xpert MTB/RIF detects both live and dead bacteria (Miotto 2012).

Xpert MTB/RIF uses molecular beacon technology to detect rifampicin resistance. Molecular beacons are nucleic acid probes that recognize and report the presence or absence of the normal, rifampicin-susceptible, 'wild type' sequence of the *rpoB* gene of TB. Five different coloured beacons are used, each covering a separate nucleic acid sequence within the amplified *rpoB* gene. When a beacon binds to the matching sequence, it fluoresces or 'lights up', which indicates the presence of one of the gene sequences that is characteristic of rifampicin-susceptible TB. Failure of the beacon to bind or delayed binding to the matching sequence indicates potential rifampicin resistance. The number and timing of detection (when the fluorescent signal rises above a pre-determined baseline cycle threshold) of positive beacons as well as results of sample processing controls allows the test to distinguish among the following results: 'No TB'; 'TB detected, rifampicin resistance detected'; 'TB detected, no rifampicin resistance detected'; and an 'invalid result' (Figure 1). A single Xpert MTB/RIF run will provide both detection of TB and detection of rifampicin resistance. One cannot deselect testing for rifampicin resistance and only run the assay for TB detection, although it is possible for the laboratory to omit results for rifampicin resistance when reporting to the healthcare provider.

Figure 1. Readout of Xpert® MTB/RIF assay for a TB positive, rifampicin-susceptible specimen. Courtesy: Karin Weyer, the Global TB Programme, WHO



1

Since Xpert MTB/RIF was released, there have been four generations (G1, G2, G3, and G4) of the test involving different software and cartridge combinations. G4 is the only Xpert MTB/RIF software and cartridge combination in current use. G4 contains modifications that improved determination of rifampicin resistance detection as previous Xpert MTB/RIF versions had found that some rifampicin susceptibility results were falsely resistant. Studies using all Xpert MTB/RIF generations are included in this updated Cochrane Review.

Clinical pathway

Patients with presumed TB or MDR-TB would undergo testing with Xpert MTB/RIF. Xpert MTB/RIF could be performed as an initial test or as an add-on test after prior testing with microscopy (WHO Policy Xpert MTB/RIF 2011). Following an Xpert MTB/RIF test, subsequent culture and drug susceptibility testing (DST) are recommended to monitor treatment progress and to detect resistance to drugs other than rifampicin (WHO Rapid Implementation 2011).

Settings of interest

We defined the settings of interest as intermediate-level and peripheral-level laboratories. The latter may be associated with primary health care facilities. We acknowledge that not all peripheral-level laboratories will be able to satisfy the operational requirements recommended for Xpert MTB/RIF, namely an uninterrupted and stable electrical power supply, temperature control, and yearly calibration of the instrument modules. However, Xpert MTB/RIF is most likely to have an impact on patient health when it is used in a setting, such as a primary health care facility, where treatment can be started as soon as possible. The level of laboratory services is not to be confused with the setting where the patient received treatment. The Global Laboratory Initiative Roadmap presents a tiered system to describe laboratory service levels: peripheral, intermediate, and central, each level with its own set of responsibilities (Global Laboratory Initiative 2010). Although three levels are described, the Roadmap recognizes that responsibilities at a given level may vary, depending on the needs of countries and diagnostic strategies. Intermediate-level laboratories typically per-

form tests such as microscopy, rapid molecular tests, culture, and DST. Peripheral-level laboratories typically perform only smear-microscopy and refer samples or patients in need of further tests, such as rapid molecular testing, culture, or DST, to a higher level laboratory (Global Laboratory Initiative 2010).

It should be noted that in the original Cochrane Review, we described the setting of interest as peripheral-level laboratories based on a different classification system previously in use (WHO Policy Framework 2010).

Role of index test(s)

We were interested in the following purposes for testing:

I. Xpert MTB/RIF for TB detection

A. Xpert MTB/RIF used as an initial test replacing smear microscopy in a population unselected by smear status

B. Xpert MTB/RIF used as an add-on test following a negative smear microscopy result

II. Xpert MTB/RIF for rifampicin resistance detection

A. Xpert MTB/RIF used as an initial test for rifampicin resistance replacing conventional phenotypic DST as the initial test

As mentioned, Xpert MTB/RIF does not eliminate the need for subsequent culture and phenotypic DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin.

Alternative test(s)

In this section, we describe selected alternative tests for detection of TB and rifampicin resistance. For a comprehensive review of these tests, we refer the reader to several excellent resources (Drobniewski 2012; Nahid 2012; UNITAID 2013).

Smear microscopy, which involves the direct examination of sputum smears with Ziehl-Neelsen staining for acid-fast bacilli (*M. tuberculosis* bacteria), is the most commonly used test for TB detection in resource-limited settings (International Standards 2009). Advantages of smear microscopy include its simplicity, low cost, speed, and high specificity in high TB burden areas. In addition, smear microscopy identifies the most infectious TB patients. Smear microscopy can be performed in basic laboratories. Drawbacks of smear microscopy include the need for specialized training and its relatively low sensitivity, 50% to 60% on average for a direct smear (Steingart 2006a). Although, the sensitivity of microscopy can be improved by approximately 10% with fluorescence (Steingart 2006), a large number of TB cases still go undiagnosed. Smear-negative TB is disproportionately higher in HIV-positive than HIV-negative individuals, accounting for 24% to 61% of all pulmonary cases in people living with HIV (Getahun 2007; Perkins 2007). Microscopy cannot distinguish between drug-susceptible TB and drug-resistant TB.

Nucleic acid amplification tests (NAATs) are molecular systems that can detect small quantities of genetic material (DNA or RNA) from microorganisms, such as *M. tuberculosis*. A variety of molecular amplification methods are available, of which PCR is the most common. NAATs are available as commercial kits and in-house tests (based on a protocol developed in a non-commercial laboratory) and are used routinely in high-income countries for TB detection. In-house PCR is widely used in developing countries because these tests are less expensive than commercial kits. However, in-house PCR is known to produce highly inconsistent results (Flores 2005). The use of NAATs has recently been recommended as standard practice in the United States (CDC 2009). The main advantage of NAATs is that they can provide results several weeks earlier than culture (CDC 2009). Drawbacks are that these tests are often too expensive and complex for routine use by TB programmes in resource-limited settings. In addition, although the specificity of NAATs is high, some NAATs have shown variable and low sensitivity, especially in sputum smear-negative patients (Flores 2005; Greco 2006; Ling 2008a).

Alternative molecular methods for DST include the commercial line probe assays, INNO-LiPA Rif.TB (Innogenetics, Ghent, Belgium) and GenoType® MTBDRplus assay (Hain LifeScience GmbH, Nehren, Germany). The INNO-LiPA Rif.TB assay targets common mutations in the *rpoB* gene associated with rifampicin resistance, while the GenoType® MTBDRplus assay also targets the common mutations in katG and inhA genes associated with isoniazid resistance in addition to the mutations in the *rpoB* gene (UNITAID 2013). Advantages of line probe assays are that they can provide a result for detection of TB and drug resistance in one to two days. Also, they have both high sensitivity (greater than 97%) and high specificity (greater than 99%) for the detection of rifampicin resistance alone, or in combination with isoniazid (sensitivity greater than 90%; specificity greater than 99%), on TB isolates and smear-positive sputum specimens (Ling 2008). Drawbacks are that line probe assays are expensive and must be used in reference laboratories (Nahid 2012). These tests have been endorsed by WHO (WHO Policy Line Probe Assays 2008).

Rationale

Xpert MTB/RIF, if accurate, would provide obvious benefits for patients (earlier diagnosis and the opportunity to begin earlier, appropriate treatment) and for public health (opportunities to interrupt TB transmission), especially in developing countries. To our knowledge, at the time of writing, one non-Cochrane systematic review on the diagnostic accuracy of Xpert MTB/RIF has been published (Chang 2012). However, the authors performed literature searching to 1 October 2011 and used statistical methods for meta-analysis other than the currently recommended bivariate random-effects models (Macaskill 2010).

WHO issued initial recommendations on the use of Xpert MTB/RIF in early 2011 (WHO Policy Xpert MTB/RIF 2011). We performed this updated Cochrane Review as part of a WHO process

to develop updated guidelines on the use of the test (WHO Xpert MTB/RIF Policy Update 2013).

OBJECTIVES

Primary objectives

Since Xpert MTB/RIF can detect both TB and rifampicin resistance, we had two review questions with the following primary objectives:

Xpert MTB/RIF for TB detection

- To determine summary estimates of the diagnostic accuracy of Xpert MTB/RIF for the diagnosis of pulmonary TB in adults

Xpert MTB/RIF for rifampicin resistance detection

- To determine summary estimates of the diagnostic accuracy of Xpert MTB/RIF for detection of rifampicin resistance in adults

Secondary objectives

Our secondary objective was to investigate heterogeneity in Xpert MTB/RIF sensitivity and specificity in relation to covariates. For TB detection, the covariates of interest were smear status; HIV status; condition of the specimens (fresh versus frozen); preparation of the specimens (unprocessed versus processed); country income status; proportion of TB cases in the study; and type of setting for running Xpert MTB/RIF (clinical or laboratory). For rifampicin resistance detection, the covariates of interest were Xpert MTB/RIF assay version and proportion of rifampicin resistant samples in the study (prevalence of rifampicin resistance in the study population).

METHODS

Criteria for considering studies for this review

Types of studies

We included primary studies that assessed the diagnostic accuracy of Xpert MTB/RIF for both pulmonary TB and rifampicin resistance, or pulmonary TB alone. Diagnostic accuracy studies are typically cross-sectional in design. However, we also searched for randomized controlled trials (RCTs) and cohort studies. We only included studies that reported data comparing Xpert MTB/RIF to an acceptable reference standard from which we could extract true positive (TP), true negative (TN), false positive (FP), and false negative (FN) values. Xpert MTB/RIF could be assessed alone or together with other tests.

We excluded studies with a case-control design because these types of studies are prone to bias, in particular, studies enrolling patients with severe disease and healthy participants without disease. We also excluded studies reported only in abstracts.

Participants

We included studies that recruited adult or predominantly adult patients, aged 15 years or older, presumed to have pulmonary TB or MDR-TB, with or without HIV infection. Also, we included studies that assessed the diagnostic accuracy of Xpert MTB/RIF using sputum and other respiratory specimens (such as fluid obtained from bronchial alveolar lavage and tracheal aspiration) consistent with the intended use of the manufacturer (Cepheid 2009), and studies from all types of health facilities and all laboratory levels (peripheral, intermediate, and central) from all countries. The majority of included studies provided data on the age of study participants. We considered it highly likely that studies that did not report age data involved all or mostly adults for the following reasons: the vast majority of specimens evaluated with Xpert MTB/RIF were sputum specimens and children have difficulty producing sputum; we excluded data on specimens obtained by gastric aspiration, as this specimen collection method is used mostly for investigating TB in children; we excluded studies that specifically evaluated the use of Xpert MTB/RIF in children; and we performed a sensitivity analysis by dropping studies that did not report age data to check whether the accuracy results changed Sensitivity analyses.

Index tests

Xpert MTB/RIF was the index test under evaluation.

We also compared Xpert MTB/RIF with smear microscopy, either Ziehl-Neelsen microscopy, fluorescence microscopy, or both microscopy methods.

Target conditions

The target conditions were active pulmonary TB and rifampicin resistance.

Reference standards

For TB, acceptable reference standards used solid media (Löwenstein-Jensen, Middlebrook 7H10 or 7H11, or Ogawa media) or a commercial liquid culture system, (such as BACTEC™ 460TB System or BACTEC™ MGIT™ 960 Mycobacterial Detection System, BD, USA; BacT/ALERT® System, bioMérieux, France; or VersaTREK® Mycobacteria Detection & Susceptibility, Thermo Fisher Scientific, USA).

For rifampicin resistance, the reference standards were phenotypic culture-based DST methods recommended by WHO (WHO Policy DST 2008). Acceptable methods were the proportion method performed on solid media (such as Löwenstein-Jensen, Middlebrook 7H10 or 7H11, or Ogawa media), use of a commercial liquid culture system (such as BACTEC™ 460TB System or BACTEC™ MGIT™ 960 Mycobacterial Detection System, BD, USA; BacT/ALERT® System, bioMérieux, France; or VersaTREK® Mycobacteria Detection & Susceptibility, Thermo Fisher Scientific, USA), or both.

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and ongoing).

Electronic searches

Vittoria Lutje, (VL) the Information Specialist for the Cochrane Infectious Diseases Group, performed searches on three occasions, 25 September 2011, 15 December 2011, and 7 February 2013. Using the strategy described in Appendix 1, she searched the following databases: Cochrane Infectious Diseases Group Specialized Register; MEDLINE; EMBASE; ISI Web of Knowledge; MEDION; LILACS; BIOSIS; and SCOPUS. She also searched the metaRegister of Controlled Trials (mRCT) and the search portal of the WHO International Clinical Trials Registry Platform, to identify ongoing trials. We limited all searches to 2007 onward because the development of Xpert MTB/RIF was completed in 2009 and the first paper describing its clinical use was published electronically in 2009 (Helb 2010). VL performed the searches without language restriction.

Searching other resources

To identify additional published, unpublished, and ongoing studies, we performed the following tasks:

- reviewed reference lists of included articles and review articles identified through the above methods;
- contacted Cepheid, the test manufacturer;
- handsearched WHO reports on Xpert MTB/RIF;
- contacted researchers at the Foundation for Innovative New Diagnostics (FIND), members of the Stop TB Partnership's New Diagnostics Working Group, and other experts in the field of TB diagnosis.

Data collection and analysis

Selection of studies

Two review authors (KRS and DJH) independently scrutinized titles and abstracts identified from electronic literature searches to identify potentially eligible studies. We retrieved the article of any citation identified by either review author for full-text review. KRS and DJH independently assessed articles for inclusion using predefined inclusion and exclusion criteria, and resolved any discrepancies by discussion between the review authors. We listed the excluded studies and the reasons for their exclusion.

We named studies according to the surname of the first author and year of publication. For multicentre studies, the study-naming scheme uniquely identified multiple study centres from within each study (for example, Boehme 2010a; Boehme 2010b), each of which reported data separately for a distinct population at a given study site. Hence, the number of study centres exceeds the number of studies.

Data extraction and management

We extracted data on the following characteristics:

- author, publication year, study design, case country of residence, country income status classified by the World Bank List of Economies (World Bank 2012), level of laboratory services, type of setting for running Xpert MTB/RIF (clinical or laboratory);
- population, age, gender, HIV status, smear status, and follow-up;
- reference standard;
- Xpert MTB/RIF assay version;
- specimen collection (such as expectorated sputum, induced sputum);
- condition of the specimen (fresh or frozen);
- preparation of the specimen (processed or unprocessed);
- QUADAS-2 items (Whiting 2011);
- data for two-by-two tables for Xpert MTB/RIF, including results reported as uninterpretable (results reported as indeterminate, invalid, error, or no result);
- time to diagnosis (time from specimen collection until there is an available TB result in laboratory or clinic);
- time to treatment initiation (time from specimen collection until time patient starts treatment).

Whenever possible, we extracted TP, FP, FN, and TN values based on one Xpert MTB/RIF result for one specimen provided by one patient. However, in some of the studies, the number of specimens (and Xpert MTB/RIF results) exceeded the number of patients, suggesting that a single patient may have provided multiple specimens. We therefore compared pooled sensitivity and specificity for TB detection in all studies with pooled sensitivity and specificity in the subset of studies that provided one Xpert MTB/RIF result based on one specimen provided by one patient (see Sensitivity analyses).

Concerning the condition of the specimen, although the manufacturer recommends use of fresh specimens, we were aware that

studies had been conducted using frozen specimens so we extracted this information as well.

Concerning the definition of smear positivity, as the vast majority of included studies performed Xpert MTB/RIF in intermediate-level or central-level laboratories, we assumed these studies adhered to the revised definition of a new sputum smear-positive pulmonary TB case based on the presence of at least one acid-fast bacillus in at least one sputum sample in countries with a well-functioning external quality assurance system (WHO Policy Smear-positive TB Case 2007).

We developed a standardized data extraction form and piloted the form with four studies. Based upon the pilot, we finalized the form. Two review authors (KRS and DH) independently extracted data from each study using the final form. We contacted study authors for missing data and clarifications and entered all data into Microsoft® Excel. The final data extraction form is in Appendix 2.

Assessment of methodological quality

We appraised the quality of included studies with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (Whiting 2011). QUADAS-2 consists of four domains: patient selection, index test, reference standard, and flow and timing. We assessed all domains for the potential for risk of bias and the first three domains for concerns regarding applicability. We used questions, called signalling questions, for each domain to form judgments about the risk of bias. As recommended, we first developed guidance on how to appraise each signalling question and interpret this information tailored to this review. Then, one review author (KRS) piloted the tool with four of the included studies. Based on experience gained from the pilot, we finalized the tool. Two review authors (KRS and DH) independently assessed the methodological quality of the included studies with the finalized tool. We presented results in the text, graphs, and a table. We did not generate a summary "quality score" because of problems associated with such numeric scores (Juni 1999; Whiting 2005). We explained definitions for using QUADAS-2 in Appendix 3.

Statistical analysis and data synthesis

We performed descriptive analyses for the results of the included studies using Stata 12 (Stata) and presented key study characteristics in Characteristics of included studies. We used data reported in the two-by-two tables to calculate sensitivity and specificity estimates and 95% confidence intervals (CI) for individual studies and to generate forest plots using Review Manager 5. Whenever possible, we included NTM as non-TB for specificity determinations. We chose to use data that were not subject to discrepant analyses (unresolved data), since resolved data after discrepant analyses are a potential for risk of bias (Hadgu 2005).

We carried out meta-analyses to estimate the pooled sensitivity and specificity of Xpert MTB/RIF separately for TB detection (I. A. and I. B.) and rifampicin resistance detection (II. A.). When possible, we determined pooled estimates using an adaptation of the bivariate random-effects model (Reitsma 2005) to allow for a hierarchical structure for the two multicentre studies (Boehme 2010; Boehme 2011). The bivariate random-effects approach allowed us to calculate the pooled estimates of sensitivity and specificity while dealing with potential sources of variation caused by (1) imprecision of sensitivity and specificity estimates within individual studies; (2) correlation between sensitivity and specificity across studies; and (3) variation in sensitivity and specificity between studies. In a few cases, namely TB detection among smear-positive individuals and rifampicin resistance detection (described below), where data were insufficient for bivariate analyses, we performed univariate analyses.

To compare the relative value of Xpert MTB/RIF and smear microscopy, we estimated the difference between their pooled sensitivities and pooled specificities. For this analysis, the specificity of smear was assumed to be 100% (Toman 2004a; Steingart 2006a). We also presented the data in a descriptive plot showing the estimates of sensitivity and specificity of Xpert MTB/RIF compared with those of smear microscopy in studies that reported on both tests.

To determine the value of Xpert MTB/RIF as a replacement test for smear (I. A.), we included studies with unselected individuals presumed to have TB to estimate pooled sensitivity and specificity. To determine the value of Xpert MTB/RIF as an add-on test (I. B.), we estimated its sensitivity and specificity among smear-negative individuals presumed to have TB. We did this by including individual studies that enrolled individuals preselected to be predominantly smear negative as well as studies providing results for unselected smear-negative individuals.

For rifampicin resistance detection, we performed univariate meta-analyses (using all available data) to determine sensitivity and specificity estimates separately. We did this because, in several studies, all patients were rifampicin susceptible (rifampicin resistance negatives), thus contributing data for specificity but not for sensitivity. We also performed a sensitivity analysis using the bivariate random-effects model for the subset of studies that provided data for both sensitivity and specificity.

We estimated all models using a Bayesian approach with non-subjective prior distributions and implemented using WinBUGS (Version 1.4.3) (Lunn 2000). Under the Bayesian approach, all unknown parameters must be provided a prior distribution that defines the range of possible values of the parameter and the likelihood of each of those values based on information external to the data. In order to let the observed data determine the final results, we chose to use low-information prior distributions over the pooled sensitivity and specificity parameters and their between-study standard deviation parameters. The model we used is summarized in the Statistical Appendix together with the WinBUGS program used to implement it (Appendix 4). Information from the prior distribution is combined with the likelihood of the ob-

served data in accordance with Bayes theorem to obtain a posterior distribution for each unknown parameter.

Using a sample from the posterior distribution, we can obtain various descriptive statistics of interest. We estimated the median pooled sensitivity and specificity and their 95% credible intervals (CrI).The median or the 50% quantile is the value below which 50% of the posterior sample lies. We reported the median because the posterior distributions of some parameters may be skewed and the median would be considered a better point estimate of the unknown parameter than the mean in such cases. The 95% CrI is the Bayesian equivalent of the classical (frequentist) 95% CI. (We have indicated 95% CI for individual study estimates and 95% CrI for pooled study estimates as appropriate). The 95% CrI may be interpreted as an interval that has a 95% probability of capturing the true value of the unknown parameter given the observed data and the prior information.

We also estimated the 'predicted' sensitivity and specificity in a future study together with their 95% CrIs. The predicted estimate is our best guess for the estimate in a future study and is the same as the pooled estimate. The CrIs, however, may be different. These values are derived from the predicted region typically reported in a bivariate meta-analysis plot. If there is no heterogeneity at all between studies, the CI (or CrI) around the predicted estimate will be the same as the CI around the pooled estimate. On the other hand, if there is considerable heterogeneity between studies, the CI around the predicted estimate will be much wider than the CI around the pooled estimate. We generated the plots using R (version 2.15.1) (R 2008).

Approach to uninterpretable Xpert MTB/RIF results

We excluded uninterpretable test results from the analyses for determination of sensitivity and specificity for both TB detection and rifampicin resistance detection. We used a hierarchical model for a single proportion to estimate the pooled proportion of uninterpretable Xpert MTB/RIF results.

Investigations of heterogeneity

I. Xpert MTB/RIF for TB detection

Effect of smear status and HIV status

We investigated heterogeneity by performing subgroup analyses to determine sensitivity and specificity estimates for patients classified by smear or HIV status. Within subgroups, we analyzed the data in two ways: 1) we performed descriptive analyses where we included all studies that provided relevant data and displayed these data in forest plots; and 2) we performed meta-analyses where we included only studies that provided data for both subgroups (for example, smear-positive and smear-negative subgroups) within the same study. In the latter head-to-head comparison, we hoped to achieve a similar distribution of other patient characteristics and manner of test execution in the subgroups. For meta-analyses, we presented pooled accuracy results in tables.

Effect of other covariates

To study the impact of additional covariates of interest, we performed meta-regression with the following covariates: condition of the specimen (fresh versus frozen), preparation of the specimen (unprocessed versus processed), proportion of TB cases in the study ($\leq$ 30% versus > 30%, proportion based on the median value in the included studies), and country income status (low- or middle-income versus high-income). We fit these models separately among smear-positive and smear-negative patients in an effort to adjust for smear status. All the aforementioned covariates were categorical, study-level covariates. We did not consider type of setting (clinical versus laboratory) due to insufficient data.

II. Xpert MTB/RIF for rifampicin resistance detection

Effect of the Xpert MTB/RIF assay version

A major source of heterogeneity in systematic reviews of diagnostic test accuracy is the difference in values used to define a positive test between studies. In the Xpert system, the basis for rifampicin resistance detection is the difference between the first (early cycle threshold) and the last (late cycle threshold) *M. tuberculosis*-specific beacon (Lawn 2011a). The original Xpert MTB/RIF system configuration reported rifampicin resistance when the difference in the cycle threshold was >3.5 cycles and rifampicin sensitive when the difference in the cycle threshold was $\leq$3.5 cycles (Xpert MTB/RIF G1 assay). After May 2010, the manufacturer modified the difference in the cycle threshold cut-off to improve Xpert MTB/RIF specificity for rifampicin resistance detection. This change affected the Xpert MTB/RIF G2 and G3 assays. Another modification was implemented in late 2011 affecting the Xpert MTB/RIF G4 assay. Therefore, we explored the effect of the Xpert MTB/RIF assay version on the sensitivity and specificity estimates for rifampicin resistance detection.

Effect of proportion rifampicin resistance in the study

We also explored the influence of the proportion rifampicin-resistant samples on the pooled sensitivity and specificity estimates by including a covariate, proportion rifampicin resistance $\leq$ 15 and > 15%, in the regression model.

Sensitivity analyses

We performed sensitivity analyses by limiting inclusion in the meta-analysis to: 1) studies that provided data by age that explicitly met the age criterion for participants; 2) studies where consecutive patients were selected; 3) studies where a single specimen yielded a single Xpert MTB/RIF result for a given patient; and 4) studies that explicitly represented the use of Xpert MTB/RIF for the diagnosis of individuals thought to have TB. In order to assess the influence of two large multicentre manufacturer-supported studies on the summary estimates, we performed an analysis excluding these studies (Boehme 2010; Boehme 2011).

Assessment of reporting bias

We chose not to carry out formal assessment of publication bias using methods such as funnel plots or regression tests because such techniques have not been helpful for diagnostic test accuracy studies (Macaskill 2010). However, Xpert MTB/RIF is produced by only one manufacturer and, as a new test for which there has been considerable attention and scrutiny, we believe reporting bias was minimal.

Other analyses

NTM

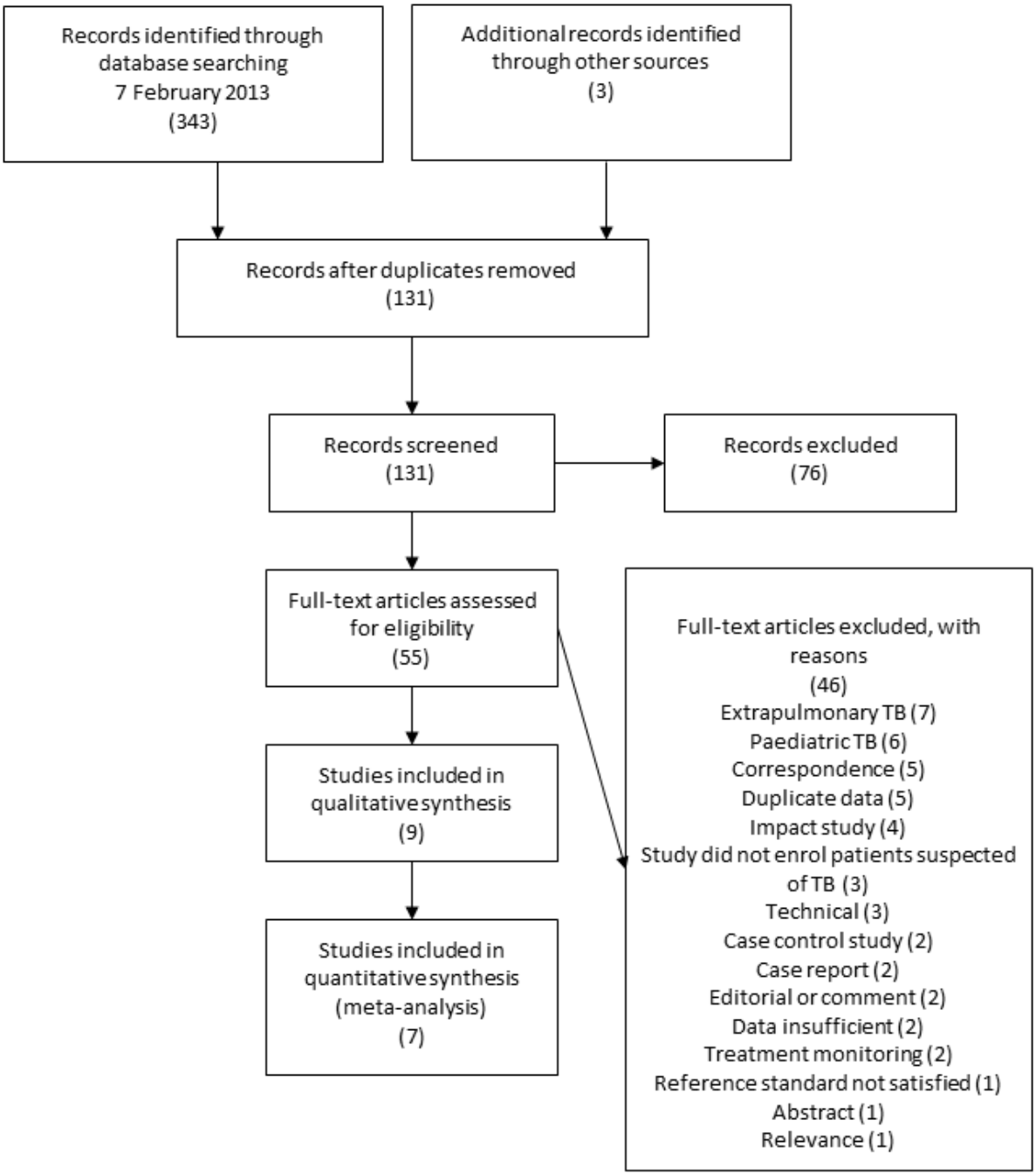
NTM, such as *M. avium* complex and *M. intracellulare*, comprise a multi-species group of human pathogens that are ubiquitous in water and soil. NTM can cause severe pulmonary and other diseases that share clinical signs with TB but are treated differently. People infected with HIV with severe immunosuppression are particularly vulnerable to infections caused by NTM (Gopinath 2010). We summarized separately data for NTM by determining the percent of false-positive Xpert MTB/RIF results in samples that grew NTMs (see Other analyses: NTM).

RESULTS

Results of the search

We identified 27 unique studies, integrating nine new studies since publication of the original Cochrane Review (Steingart 2013). Of the 27 studies, two were international multicentre studies (Boehme 2010; Boehme 2011) carried out at five and six study centres, respectively. The two studies by Boehme involved different patients. We presented descriptive characteristics and the methodological quality assessment at both study and study centre levels, and meta-analysis results at study level. One other study, conducted at three sites, reported accuracy data for the three sites combined; we considered this to be a single study and a single study centre (Marlowe 2011). Hence there were 27 studies representing 36 study centres. Figure 2 shows the flow of studies in the updated literature search. Characteristics of excluded studies lists studies excluded in this update and the original Cochrane Review.

Figure 2. Flow diagram of studies in the review



Methodological quality of included studies

Figure 3 shows the overall risk of bias and applicability concerns for the 36 study centres. Figure 4 presents the quality assessment results for the individual study centres. In the patient selection domain, 27 study centres (75%) were at low risk of bias because the centre enrolled participants consecutively and avoided inappropriate exclusions. The remaining study centres were at (1) high risk of bias because either the manner of patient selection was by convenience (Bowles 2011; Hanif 2011; Ioannidis 2011; Malbruny 2011; Marlowe 2011; Miller 2011) or the study preselected smear-positive patients (Friedrich 2011; Williamson 2012), or (2) unclear risk of bias because the manner of patient selection was not stated (Ciftci 2011). With regard to applicability (patient selection domain), 24 of the 36 study centres (67%), corresponding to 16 of the 27 studies (59%), were of low concern because these study centres evaluated sputum specimens and ran Xpert MTB/RIF in intermediate-level or peripheral-level laboratories associated with primary care clinics (Hanrahan 2013; Van Rie 2013). We judged the remaining study centres as follows: high concern, two that mainly evaluated bronchial aspirates (Al-Ateah 2012; Marlowe 2011) and one that ran Xpert MTB/RIF as a screening test (Lawn 2011), or unclear concern, nine that ran Xpert MTB/RIF in a central-level laboratory (Boehme 2010a; Boehme 2010d; Bowles 2011; Hanif 2011; Ioannidis 2011; Kurbatova 2013; Marlowe 2011; Rachow 2011; Teo 2011). In the index test (Xpert MTB/RIF) domain, we considered all study centres to be at low risk of bias and low concern regarding applicability. In the reference standard domain, we judged 33 study centres (92%) to be at low risk of bias for TB and 34 study centres (94%) to be at low risk of bias for rifampicin resistance because the reference standard results were interpreted without knowledge of the results of the Xpert MTB/RIF assay. Applicability was of low concern for all studies in the reference standard domain. In the flow and timing domain, 31 study centres (86%) were at low risk of bias because all patients were accounted for in the analysis and information about uninterpretable results was provided. We had nearly complete information for all study centres.

Figure 3. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across the 36 included study centres (27 studies). The reference standard domain pertains to TB as the target condition. See text for the reference standard relating to rifampicin resistance.

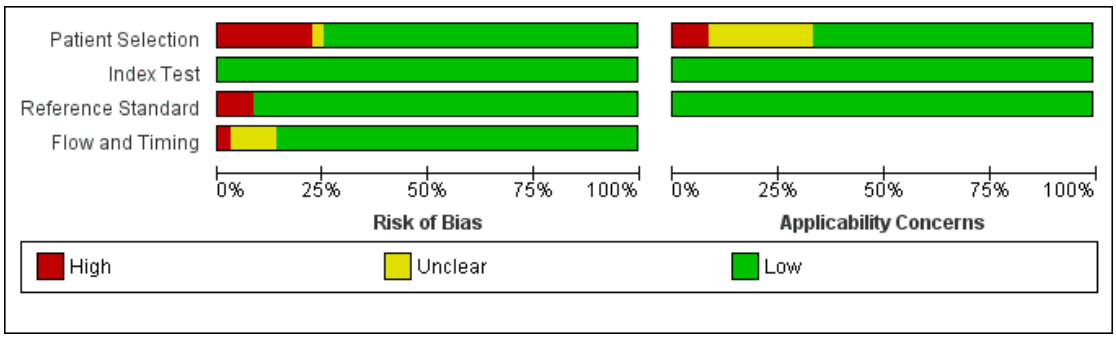
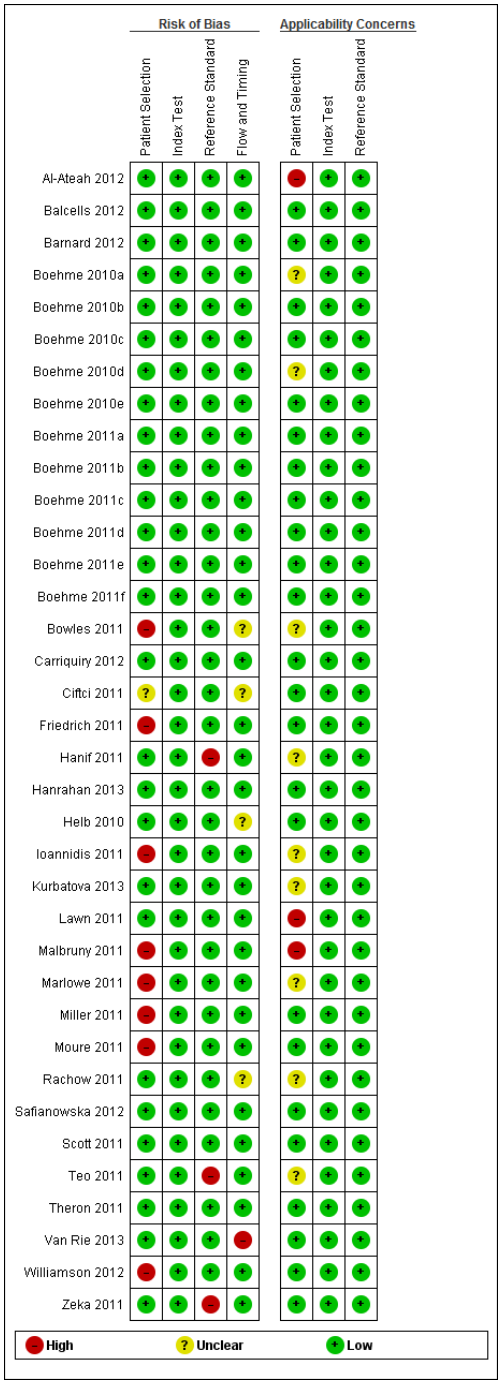


Figure 4. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study centre.



Findings

For TB detection, the 27 studies included 9557 participants. The median number of participants in the studies was 145 (Interquartile range (IQR) 99 to 211). The proportion of TB cases in the studies ranged from 4.0% (Hanif 2011) to 100% (Friedrich 2011), median 34.4% (IQR 23.1 to 57.4).

Of the 27 studies, 24 studies (33 study centres) including 2966 participants provided data for rifampicin resistance detection. Of the three studies that were not included, one study presented combined results for pulmonary and extrapulmonary specimens (Moure 2011); one study did not report information on rifampicin resistance (Helb 2010); and one study did not use the defined reference standard (Barnard 2012). Seven studies detected no rifampicin resistance with the reference standard (Al-Ateah 2012; Ciftci 2011; Hanif 2011; Marlowe 2011; Rachow 2011; Safianowska 2012; Van Rie 2013). The proportion of rifampicin resistant samples in the studies ranged from 0.0% to 56.6% (Kurbatova 2013), median 3.2% (IQR 0.0 to 13.2).

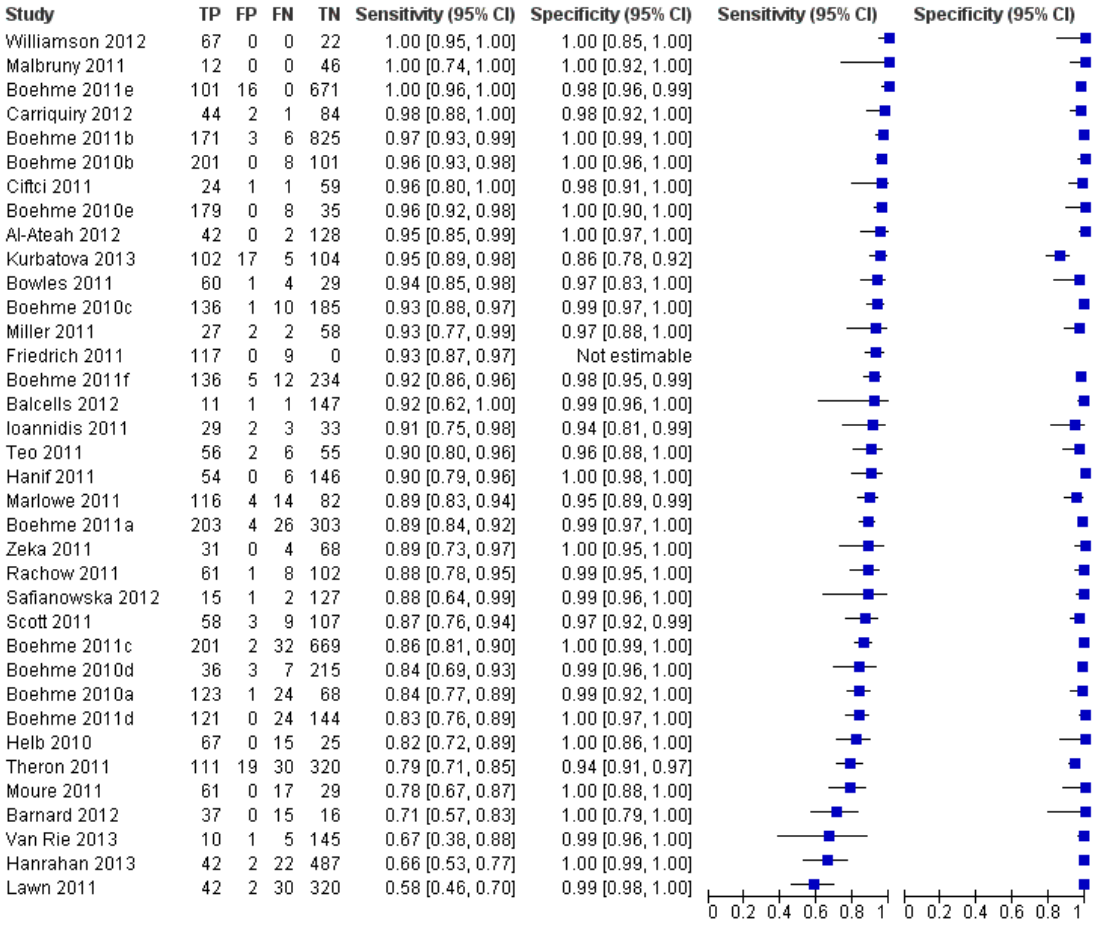
Characteristics of included studies presents key characteristics for the 27 studies. All 27 studies used a cross-sectional study design for determining the diagnostic accuracy of Xpert MTB/RIF. The majority of studies evaluated expectorated sputum. Sixteen studies (59%), corresponding to 25 study centres (69%), were located in low-income or middle-income countries. In the countries represented by the 36 study centres, TB incidence rates per 100,000 population ranged from 3.9 (USA) to 993 (South Africa). Percent MDR-TB among new TB cases ranged from 0% (Kuwait) to 22% (Azerbaijan) and among retreatment cases ranged from 0% (Singapore, Tanzania) to 56% (Azerbaijan) (WHO Drug Resistance 2008; WHO M/XDR-TB 2010; Wright 2009; Zignol 2012).

I. Xpert MTB/RIF for TB detection

A. Xpert MTB/RIF used as an initial test replacing smear microscopy in a population unselected by smear status

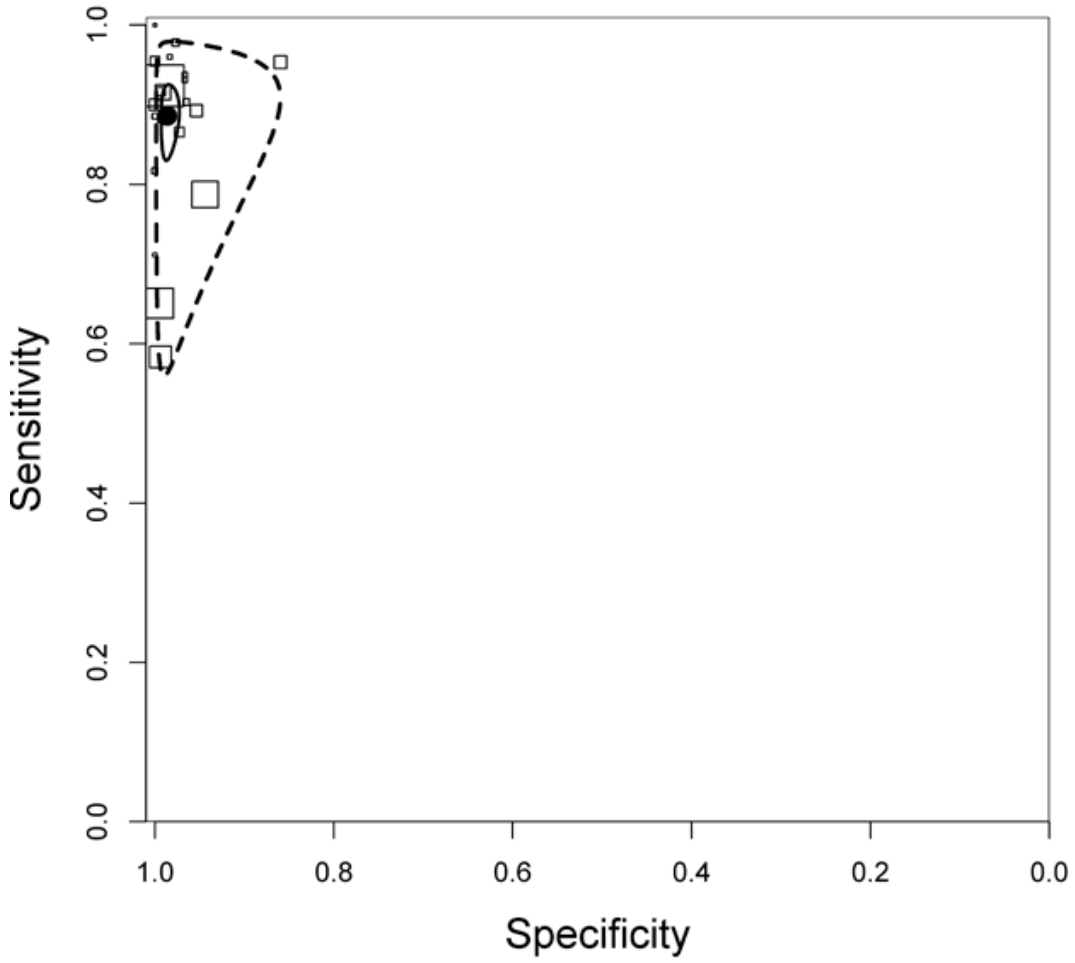
We have presented forest plots of Xpert MTB/RIF sensitivity and specificity for TB detection for the 27 studies (36 study centres) in Figure 5. Sensitivity estimates ranged from 58% to 100% and specificity estimates ranged from 86% to 100%.

Figure 5. Forest plots of Xpert MTB/RIF sensitivity and specificity for TB detection, Xpert MTB/RIF used as an initial test replacing smear microscopy. The individual studies are ordered by decreasing sensitivity. TP = True Positive; FP = False Positive; FN = False Negative; TN = True Negative. Between brackets are the 95% CI of sensitivity and specificity. The figure shows the estimated sensitivity and specificity of the study (blue square) and its 95% CI (black horizontal line). Xpert MTB/RIF specificity could not be estimated in one study.



We included 22 of the total 27 studies (8998 participants) in this meta-analysis. We excluded five studies that enrolled primarily only smear-positive or smear-negative patients (Friedrich 2011; Ioannidis 2011; Moure 2011; Van Rie 2013; Williamson 2012). For TB detection, Xpert MTB/RIF pooled sensitivity and specificity were 89% (95% CrI 85% to 92%) and 99% (95% CrI 98% to 99%), respectively (Table 1). The predicted sensitivity and specificity of Xpert MTB/RIF for TB detection were 89% (95% CrI 63% to 97%) and 99% (95% CrI 90% to 100%), respectively. In relation to the pooled values, the wider 95% CrIs around the predicted values suggested some variability between studies, particularly in sensitivity (Table 1). Figure 6 presents the pooled and predicted sensitivity and specificity estimates together with the credible and prediction regions for Xpert MTB/RIF for TB detection. The summary point appears close to the upper left-hand corner of the plot, suggesting high accuracy of Xpert MTB/RIF for TB detection. The 95% credible region around the summary (pooled) value of sensitivity and specificity, the region that contains likely combinations of the pooled sensitivity and specificity, is relatively narrow. The 95% prediction region is wider, displaying more uncertainty as to where the likely values of sensitivity and specificity might occur in a future study.

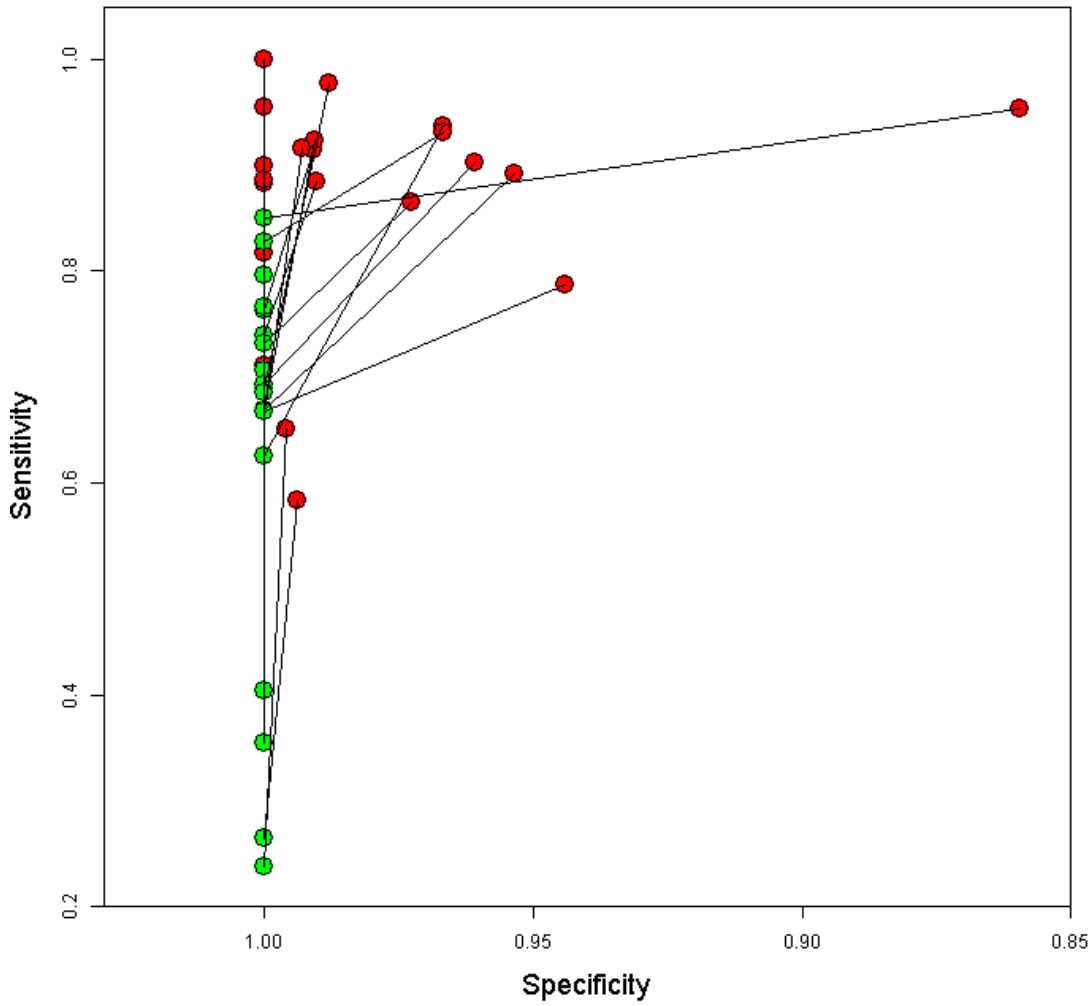
Figure 6. Summary plots of Xpert MTB/RIF sensitivity and specificity for TB detection, Xpert MTB/RIF used as an initial test replacing smear microscopy. Each individual study is represented by an empty square. The size of the square is proportional to the sample size of the study such that larger studies are represented by larger squares. The filled circle is the median pooled estimate for sensitivity and specificity. The solid curves represent the 95% credible region around the summary estimate; the dashed curves represent the 95% prediction region.



TB detection, Xpert MTB/RIF compared with smear microscopy

Twenty-one studies (8880 participants) provided data from which to compare the sensitivity of Xpert MTB/RIF and smear microscopy. Figure 7 displays results of smear microscopy versus Xpert MTB/RIF for the individual studies. In the meta-analysis, the sensitivity estimate for Xpert MTB/RIF was the same as the estimate in the meta-analysis in I. A., the difference in the number of studies and participants being due to use of the subset of studies that also reported results by smear status. For smear microscopy, the pooled sensitivity was 65% (95% CrI 57% to 72%). For Xpert MTB/RIF, the pooled sensitivity was 88% (95% CrI 84% to 92%). Therefore, in comparison with smear microscopy, Xpert MTB/RIF increased TB detection among culture-confirmed cases by 23% (95% CrI 15% to 32%).

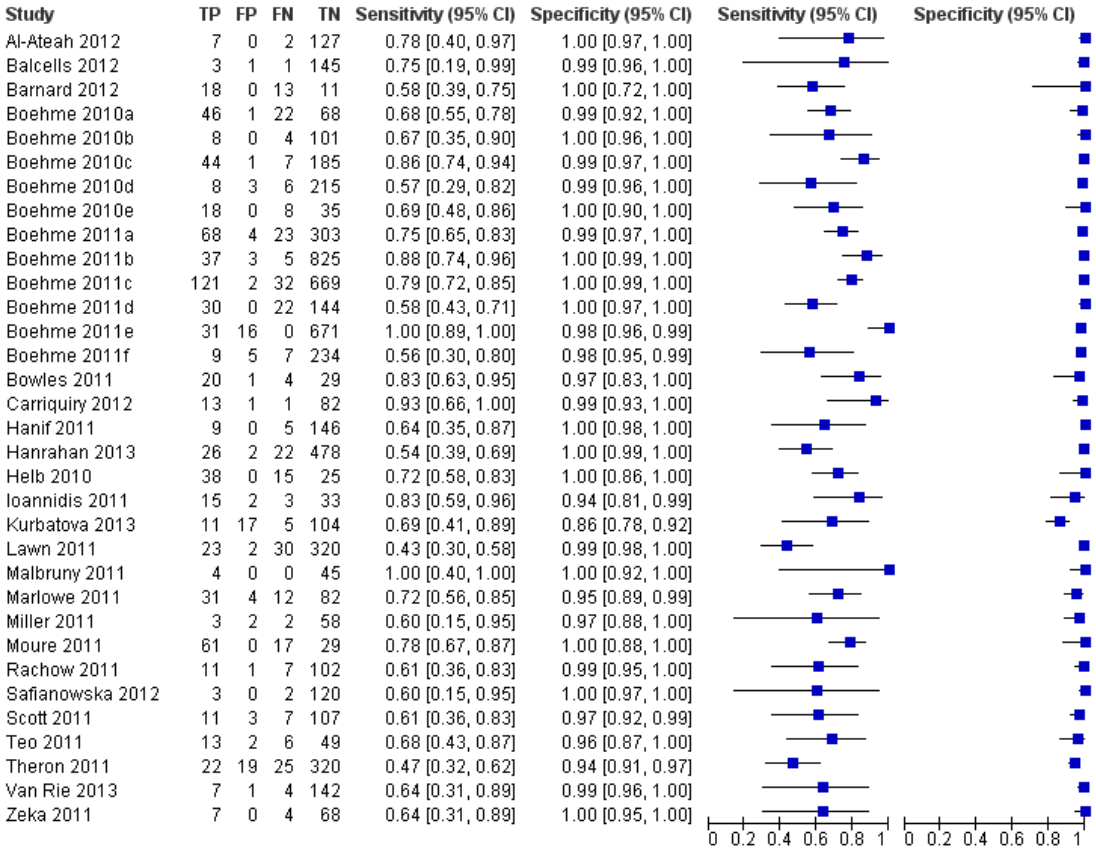
Figure 7. Study results of smear microscopy (green circle) versus Xpert MTB/RIF (red circle) plotted in ROC space. The specificity of smear was assumed to be 100%.



B. Xpert MTB/RIF used as an add-on test following a negative smear microscopy result

Three studies performed microscopy and, for those patients found to be smear-negative, subsequently ran Xpert MTB/RIF (Ioannidis 2011; Moure 2011; Van Rie 2013). Two of these studies were laboratory-based assessments performed in high-income countries (Ioannidis 2011; Moure 2011). One study performed Xpert MTB/RIF at a primary care clinic in a low-income country (Van Rie 2013). For the three studies, sensitivities ranged from 64% to 83% and specificities from 94% to 100% (Figure 8).

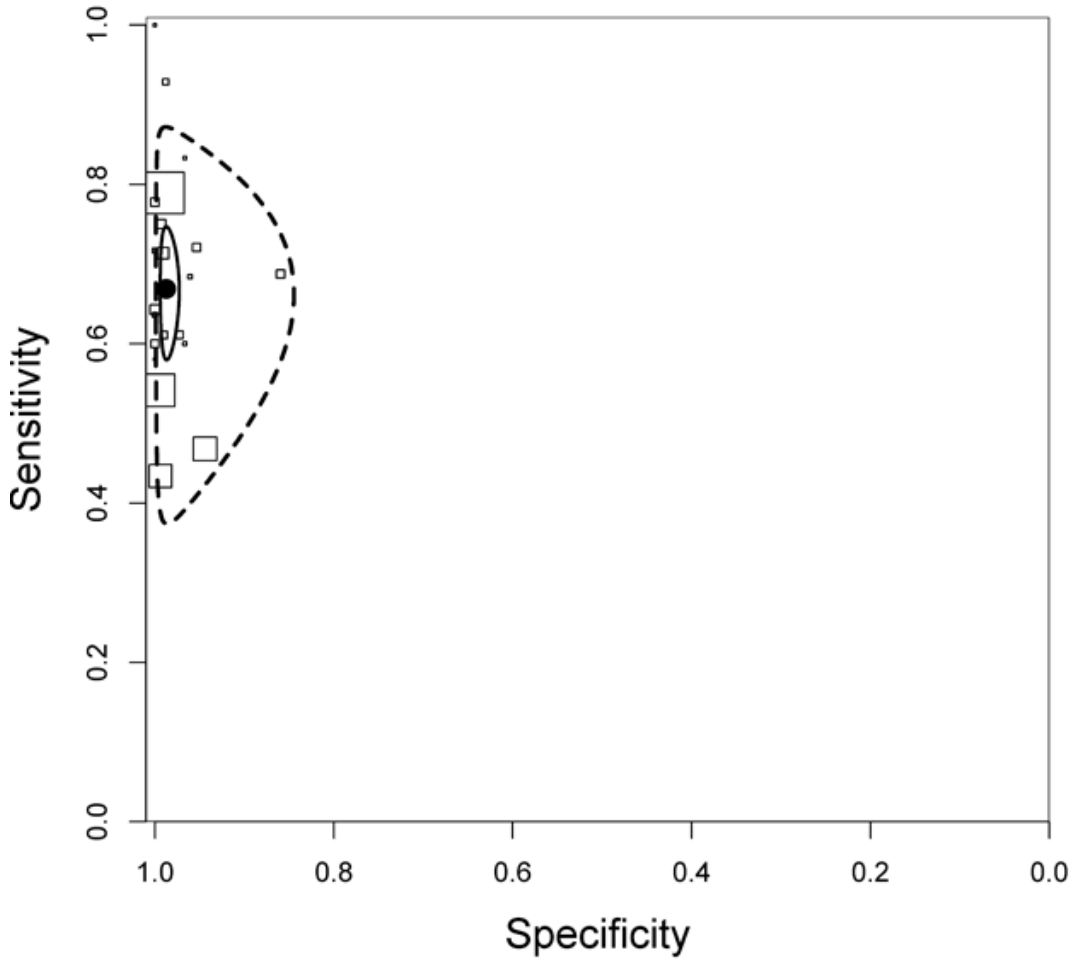
Figure 8. Forest plots of Xpert MTB/RIF for TB detection in studies reporting data for smear-negative patients. We also used these data as a proxy for the accuracy of Xpert MTB/RIF used as an add-on test following a negative smear microscopy result. TP = True Positive; FP = False Positive; FN = False Negative; TN = True Negative. Between brackets the 95% CI of sensitivity and specificity. The figure shows the estimated sensitivity and specificity of the study (blue square) and its 95% CI (black horizontal line).



In the meta-analysis, the pooled sensitivity was 67% (95% CrI 60% to 74%) and the pooled specificity was 99% (95% CrI 98% to 99%; 21 studies, 6950 participants; Table 1). Therefore, 67% of smear-negative culture-confirmed TB cases were detected using Xpert MTB/RIF following smear microscopy, increasing case detection by 67% (95% CrI, 60% to 74%) in this group.

Figure 9 presents the pooled and predicted sensitivity and specificity estimates together with the credible and prediction regions for this analysis. The summary point is relatively far from the upper left-hand corner of the plot, suggesting lower accuracy of Xpert MTB/RIF when used as an add-on test than as a replacement test. The 95% credible region around the summary value of sensitivity and specificity is relatively wide.

Figure 9. Summary plots of Xpert MTB/RIF sensitivity and specificity for TB detection, Xpert MTB/RIF used as an add-on test following a negative smear microscopy result. Each individual study is represented by an empty square. The size of the square is proportional to the sample size of the study such that larger studies are represented by larger squares. The filled circle is the median pooled estimate for sensitivity and specificity. The solid curve represents the 95% credible region around the summary estimate; the dashed curves represent the 95% prediction region.



Uninterpretable results

Of the total 27 studies, seven studies (Al-Ateah 2012; Hanif 2011; Hanrahan 2013; Miller 2011; Moure 2011; Williamson 2012; Zeka 2011) reported zero uninterpretable results and four studies (Bowles 2011; Ciftci 2011; Helb 2010; Rachow 2011) did not provide information about uninterpretable results. Of 11,408 tests performed, the pooled proportion of uninterpretable test results was very low (1.0%, 95% CrI 0.05% to 2.0%).

Investigations of heterogeneity, TB detection

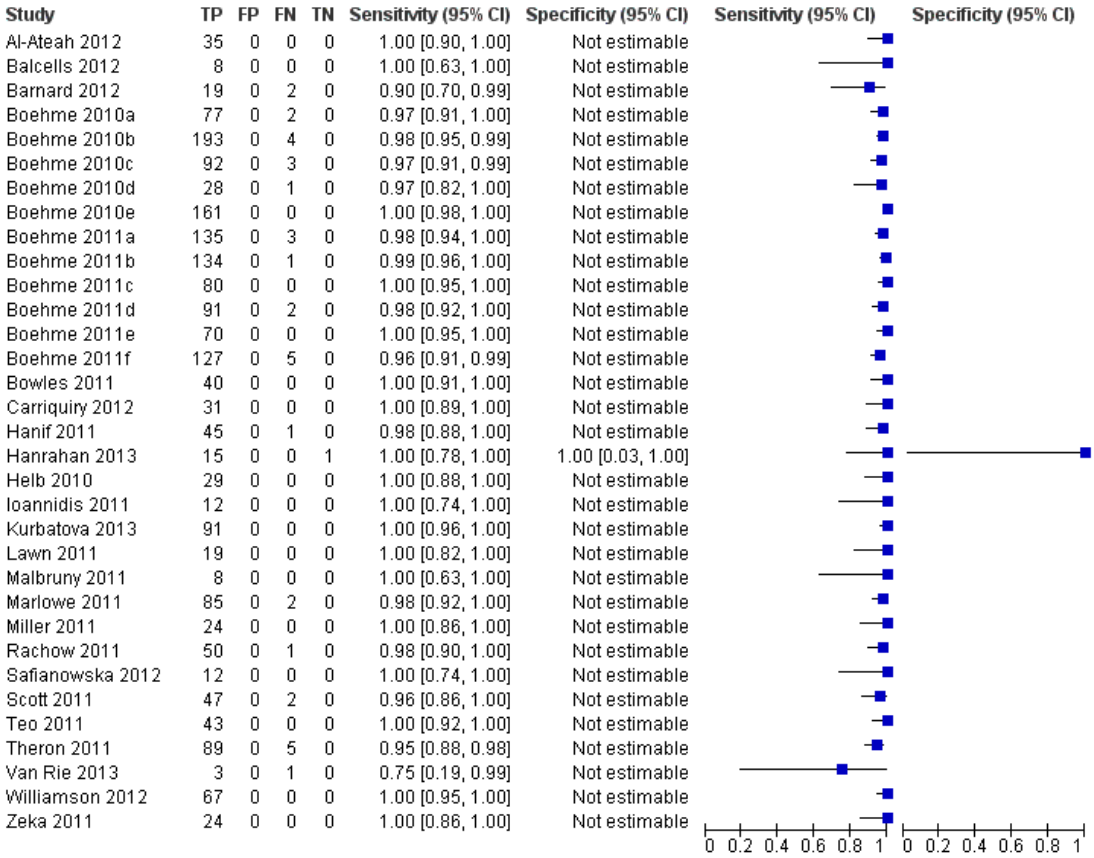
It is possible that the accuracy of Xpert MTB/RIF in clinical subgroups of patients could differ causing heterogeneity in Xpert MTB/RIF performance. We therefore determined sensitivity and specificity estimates for patients grouped by smear or HIV status.

TB detection in smear-positive and smear-negative individuals presumed to have TB

Smear-positive TB

Figure 10 displays the forest plots for studies reporting data for smear-positive patients (24 studies, 33 study centres, 2020 participants). There was little heterogeneity in the sensitivity estimates (range 95% to 100%). In the meta-analysis, the pooled sensitivity for smear-positive, culture-positive TB was 98% (95% CrI 97% to 99%; 21 studies, 1936 participants; Table 2). We did not include Van Rie 2013 in the meta-analysis as this study preselected smear-negative patients, though it did report a sensitivity estimate for Xpert MTB/RIF of 75% among four smear-positive patients. We did not estimate Xpert MTB/RIF pooled specificity in the studies in the smear-positive subgroup because almost all participants were considered to be true TB positive.

Figure 10. Forest plot of Xpert MTB/RIF sensitivity for TB detection in studies reporting data for smear-positive patients. The squares represent the sensitivity and specificity of one study, the black line its CI. TP = true positive; FP = false positive; FN = false negative; TN = true negative. Xpert MTB/RIF specificity could not be estimated in these studies.



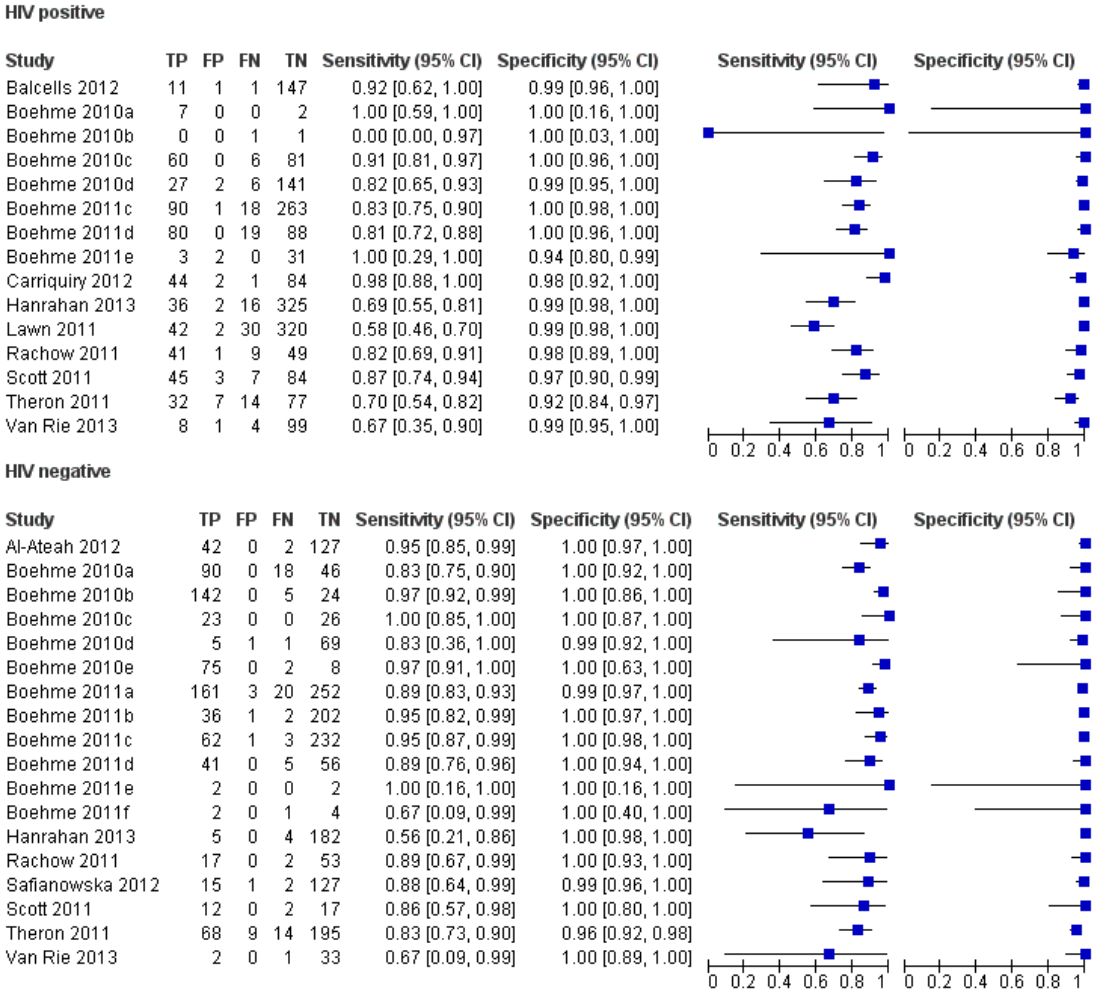
Smear-negative TB

Figure 8 displays the forest plots for studies reporting data for smear-negative patients (24 studies, 33 study centres, 7264 participants). There was considerable variability in sensitivity estimates (range 43% to 100%). Specificity estimates showed less variability (range 86% to 100%). Lawn 2011 yielded the lowest sensitivity. This study used Xpert MTB/RIF as a TB screening test in HIV-infected patients with advanced immunodeficiency enrolling in antiretroviral therapy services. The meta-analysis included 21 studies. The pooled sensitivity estimate for smear-negative, culture-positive TB was 67% (95% CrI 60% to 74%), considerably lower than the pooled sensitivity estimate for smear-positive, culture-positive TB which was 98% (95% CrI 97% to 99%; Table 2).

TB detection in HIV-negative and HIV-positive individuals presumed to have TB

Figure 11 displays the forest plots for studies reporting data for HIV-negative individuals (nine studies, 18 study centres, 2555 participants) and HIV-positive individuals (10 studies, 16 study centres, 2474 participants). Sensitivity was variable in both the HIV-negative subgroup (56% to 100%) and HIV-positive subgroup (0% to 100%). The small number of participants in several studies may have contributed to some of this variability. Specificity varied less than sensitivity in both subgroups: 96% to 100% in the HIV-negative subgroup and 92% to 100% in the HIV-positive subgroup.

Figure 11. Forest plots of Xpert MTB/RIF sensitivity and specificity for TB detection in HIV-positive and HIV-negative subgroups. The squares represent the sensitivity and specificity of one study and the black line represent its CI. TP = true positive; FP = false positive; FN = false negative; TN = true negative.



The meta-analysis included seven studies that provided data for both HIV-negative (1470 participants) and HIV-positive (1789 participants) individuals (Boehme 2010; Boehme 2011; Hanrahan 2013; Rachow 2011; Scott 2011; Theron 2011; Van Rie 2013). The pooled sensitivity was 86% (95% CrI 76% to 92%) in the HIV-negative subgroup and 79% (95% CrI 70% to 86%) in the HIV-positive subgroup (Table 2). Corresponding pooled specificities were similar: 99% (95% CrI 98% to 100%) and 98% (95% CrI 96% to 99%), respectively (Table 2). When adjusting for the percentage of smear-positive patients in each study, the impact of HIV decreased suggesting that some of the differences between the HIV-positive and HIV-negative subgroups could be attributed to differences in smear status (Table 2).

TB detection among HIV-positive individuals by smear status

Four studies reported data from which to assess the accuracy of Xpert MTB/RIF in HIV-positive individuals by smear status (Balcells 2012; Carriquiry 2012; Lawn 2011). Among people with HIV, Xpert MTB/RIF pooled sensitivity was 61% (95% CrI 40% to 81%) for smear-negative, culture-positive TB compared with 97% (95% CrI 90% to 99%) for smear-positive, culture-posi-

tive TB, a statistically significant result (Table 2). Hence, among people with HIV-TB coinfection, people with HIV infection and smear-positive disease were more likely to be diagnosed with TB using Xpert MTB/RIF than those with HIV infection and smear-negative disease.

Effect of condition of the specimen

As mentioned above, although the manufacturer recommends use of fresh specimens, we were aware that studies had been conducted using frozen specimens; therefore we explored the effect of the condition of the specimen on Xpert MTB/RIF performance. The pooled sensitivities and specificities were slightly higher for fresh specimens compared with frozen specimens within both the smear-positive and smear-negative groups, however there was considerable overlap in the CrIs around these estimates (Table 2).

Effect of specimen preparation

The pooled sensitivity was higher for unprocessed specimens compared with processed specimens in smear-negative patients, though there was considerable overlap in the CrIs around these estimates (Table 2).

Effect of the proportion of culture-confirmed TB cases in the study

For this analysis, we used a cutoff of 30% TB cases because 30% was around the median proportion of TB cases in the included studies. Within smear-negatives, the pooled sensitivity was higher for studies with a higher proportion of TB cases; however there was considerable overlap in the CrIs around these estimates (Table 2).

Effect of country income status

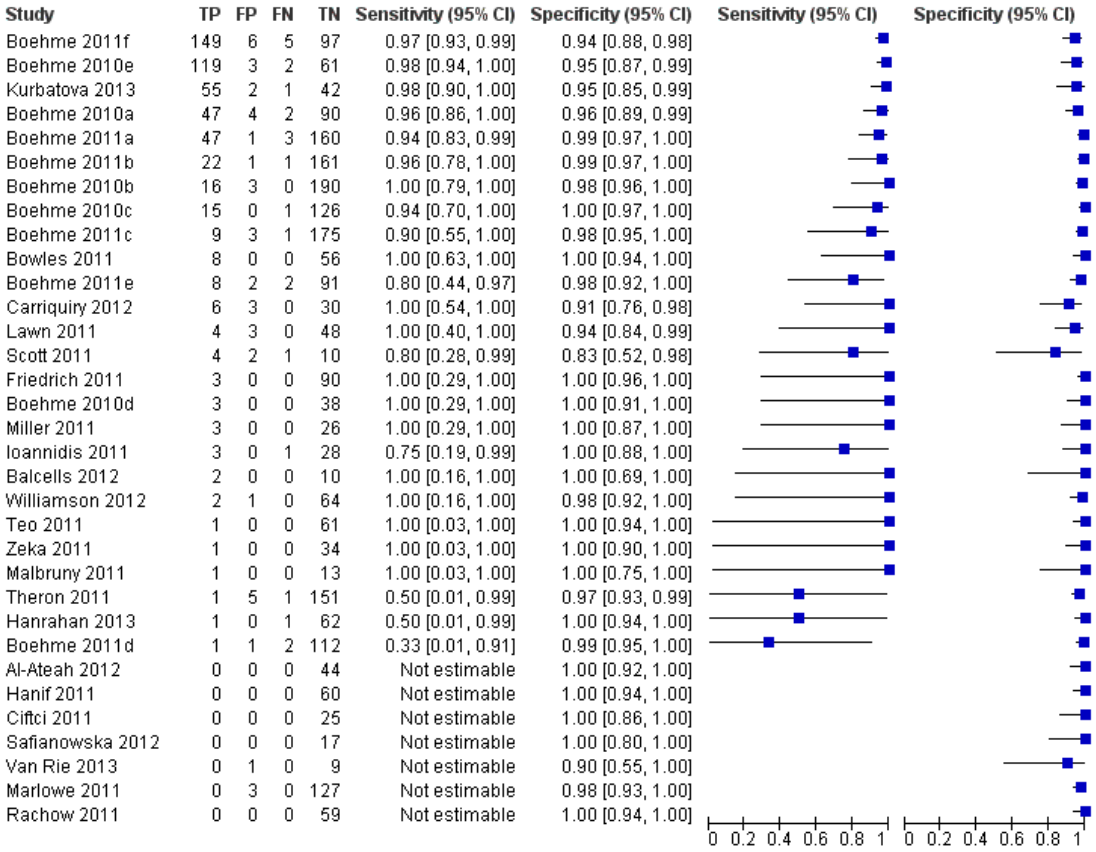
There did not appear to be an important difference in the pooled sensitivity of Xpert MTB/RIF according to country income status after adjusting for smear status (Table 2).

II. Rifampicin resistance detection

A. Xpert MTB/RIF used as an initial test replacing conventional DST

The 24 studies (33 study centres) in this analysis included 555 rifampicin-resistant specimens, median two specimens (range 1 to 250). Two studies accounted for the majority (82%, 455/555) of the rifampicin-resistant specimens (Boehme 2010; Boehme 2011). Seven studies contributed only specificity data (presence of rifampicin-susceptible TB) (Al-Ateah 2012; Ciftci 2011; Hanif 2011; Marlowe 2011; Rachow 2011; Safianowska 2012; Van Rie 2013) but not sensitivity data (presence of rifampicin-resistant TB). Figure 12 shows the forest plots of sensitivity and specificity for this analysis. The individual study centres in the plots are ordered by decreasing sensitivity and decreasing number of true positive results. Although, there was heterogeneity in sensitivity estimates (ranging from 33% to 100%), in general there was less variability among study centres with a higher number of rifampicin-resistant specimens. Specificity showed less variability than sensitivity, ranging from 83% to 100%. The pooled sensitivity and specificity by univariate analysis were 95% (95% CrI 90% to 97%) and 98% (95% CrI 97% to 99%), respectively (Table 1).

Figure 12. Forest plots of Xpert MTB/RIF sensitivity and specificity for detection of rifampicin resistance, Xpert used as an initial test replacing conventional DST as the initial test. The individual studies are ordered by decreasing sensitivity and decreasing number of true positives. The squares represent the sensitivity and specificity of one study, the black line its CI. TP = true positive; FP = false positive; FN = false negative; TN = true negative.



Investigations of heterogeneity, rifampicin resistance detection

Effect of the Xpert MTB/RIF assay version

A major source of heterogeneity in systematic reviews of diagnostic test accuracy is the difference in values used to define a positive test between studies. The basis for rifampicin resistance detection in the Xpert MTB/RIF system is the difference between the first (early cycle threshold) and the last (late cycle threshold) *M. tuberculosis*-specific beacon (Lawn 2011a). This difference is referred to as the delta cycle threshold. The original Xpert MTB/RIF system configuration reported rifampicin resistance when the delta cycle threshold was > 3.5 cycles and rifampicin sensitive when the delta cycle threshold was ≤ 3.5 cycles (Xpert MTB/RIF G1 assay). After May 2010, the manufacturer modified the delta cycle threshold cut-off to improve Xpert MTB/RIF specificity for rifampicin resistance detection (Xpert MTB/RIF G2 and G3 assays). Another modification was implemented in late 2011 (Xpert MTB/RIF G4 assay). G4 is now the only cartridge available for use.

Therefore, we explored the effect of the Xpert MTB/RIF version on the sensitivity and specificity estimates for rifampicin resistance detection. The pooled sensitivity was 93% (95% CrI 87% to 97%) for studies using Xpert MTB/RIF G2, G3, or G4 assays (13 studies) and 97% (95% CrI 91% to 99%) for studies using Xpert MTB/RIF G1 assay (four studies) (Table 3). The corresponding pooled specificities were 98% (95% CrI 96% to 99%; 16 studies) and 99% (95% CrI 98% to 100%; seven studies) (Table 3). Thus,

when G1 alone was compared with a set containing the later Xpert MTB/RIF versions, there was considerable overlap between the accuracy estimates for the different Xpert MTB/RIF versions and no apparent difference between them.

Xpert MTB/RIF G4 assay effect on specificity

One study used Xpert MTB/RIF G4 assay and provided data for specificity determinations (Kurbatova 2013). Kurbatova 2013 found a specificity of 95% (42/44; 95% CI 85% to 99%) (Figure 12).

Effect of proportion rifampicin resistant samples in the study

For this analysis, we used a cutoff of 15% for the proportion of rifampicin resistant samples in the study. The pooled sensitivity was 96% (95% CrI 91% to 98%) for studies with proportion rifampicin resistance > 15%, higher than the pooled sensitivity of 91% (95% CrI 79% to 97%) for studies with proportion rifampicin resistance ≤ 15%. The corresponding pooled specificities were 97% (95% CrI 94% to 99%) and 99% (95% CrI 98% to 99%) (Table 3). The differences in Xpert MTB/RIF sensitivity and specificity were not significantly different from 0 (Table 3).

Sensitivity analyses

For TB detection, we undertook sensitivity analyses by limiting inclusion in the meta-analysis to: 1) studies that provided age data that met our inclusion criterion for adults; 2) studies that used consecutive sampling; 3) studies where a single specimen yielded a single Xpert MTB/RIF result for a given individual; and 4) studies that explicitly tested individuals with presumed TB. We also performed a sensitivity analysis by excluding from the meta-analysis the two large multicentre studies (Boehme 2010; Boehme 2011). These sensitivity analyses made no difference to any of the findings (Table 4).

Other analyses

NTM

Fourteen studies (2626 participants) provided data on a variety of NTM that grew from the specimens tested to look for evidence of cross-reactivity: one NTM (Al-Ateah 2012); four NTM (Barnard 2012); six NTM (Bowles 2011); one NTM (Ioannidis 2011); one NTM (Kurbatova 2013); 41 NTM (Marlowe 2011); 20 NTM (Moure 2011); 45 NTM (Rachow 2011); seven NTM (Safianowska 2012); five NTM (Scott 2011); 13 NTM (Teo 2011); eight NTM (Theron 2011); three NTM (Van Rie 2013); and 22 NTM (Williamson 2012). Among these 14 studies comprising 180 NTM, Xpert MTB/RIF was positive in only one (0.6%) specimen that grew NTM (Rachow 2011).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Test result	Number of results per 1000 adults with presumed pulmonary TB (95% CrI)							
	Prevalence 2.5%		Prevalence 5%		Prevalence 10%		Prevalence 30%	
	Smear Microscopy	Xpert MTB/RIF	Smear Microscopy	Xpert MTB/RIF	Smear Microscopy	Xpert MTB/RIF	Smear Microscopy	Xpert MTB/RIF
True positives	16 (14, 18)	22 (21, 23)	33 (29, 36)	44 (42, 46)	65 (57, 72)	88 (84, 92)	195 (171, 216)	264 (252, 276)
Mean absolute difference in true positives	6 more		11 more		23 more		69 more	
False negatives	9 (7, 11)	3 (2, 4)	18 (14, 22)	6 (4, 8)	35 (28, 43)	12 (8, 16)	105 (84, 129)	36 (24, 48)
Mean absolute difference in false negatives	6 less		12 less		23 less		69 less	

Review question: What is the diagnostic accuracy of Xpert MTB/RIF assay for detection of rifampicin resistance?
Patients/population: Adults with confirmed TB
Role: Xpert MTB/RIF assay as an initial test replacing conventional phenotypic DST
Index test: Xpert MTB/RIF assay
Reference standards: Phenotypic culture-based DST
Studies: Cross-sectional
Setting: Mainly intermediate level laboratories

Type of analysis	Effect (95% credible interval)	No. of participants (studies)	Test result	Number of results per 1000 patients tested (95% CrI)[1]	
				Prevalence 5%	Prevalence 15%
Rifampicin resistance detection, Xpert MTB/RIF used as an initial test replacing conventional DST	Median pooled sensitivity 95% (90, 97) and median pooled specificity 98% (97, 99)	Median pooled sensitivity 555 (17) Median pooled specificity 2411 (24)	True Positives False Negatives False Positives True Negatives	48 (45, 49) 3 (2, 5) 19 (10, 29) 931 (922, 941)	143 (135, 146) 8 (5, 15) 17 (9, 26) 833 (825, 842)

1. The WHO suggested prevalence levels: 5% is considered equivalent to the upper limit for rifampicin resistance prevalence in new cases; 15% is considered equivalent to the lower limit for rifampicin resistance prevalence in previously treated cases.

DISCUSSION

This updated Cochrane Review on the diagnostic accuracy of Xpert MTB/RIF for TB detection and rifampicin resistance detection in adults summarizes the current literature and integrates nine new studies (33% of the included papers) identified since the original Cochrane Review (Steingart 2013). The findings in this update are consistent with those reported previously.

In adults presumed to have TB, with or without HIV infection, we found Xpert MTB/RIF to be sensitive and specific for TB detection. Xpert MTB/RIF may also be valuable as an add-on test following smear microscopy (sensitivity 67%). When used as an initial test replacing phenotypic culture-based DST, we found Xpert MTB/RIF provides accurate results for rifampicin resistance detection.

Sensitivity and specificity depend on the performance of a test in a particular situation, defined by the population, the setting, and prior testing. In a different population or setting or with a different testing strategy, the sensitivity and specificity are likely to change (Bossuyt 2008). Overall, we had low concern about applicability. Of note, a recent RCT found that Xpert MTB/RIF run by nurses at point-of-care in primary care clinics obtained similar sensitivity 83.3% (95% CI 77.2% to 88.0%) to that achieved when Xpert MTB/RIF was performed by laboratory technicians in central level laboratories 83.2% (95% CI 79.0% to 86.8%) (Theron 2013).

We found Xpert MTB/RIF sensitivity for TB detection to be higher in fresh specimens than in frozen specimens. Although we did not find conclusive evidence, one possible explanation for this observation is that investigators may have used an increased amount of buffer volume to resuspend frozen sputum specimens causing a dilution effect (Scott 2011). We also found that, in comparison with processed specimens, unprocessed specimens had slightly higher sensitivity in smear-negative patients. In addition, we found higher pooled accuracy of Xpert MTB/RIF in studies performed in high-income countries than in low- or middle-income countries. However, after adjustment for smear status, the strength of these associations decreased. Therefore, there was no conclusive evidence supporting the impact of either specimen preparation or country income on Xpert MTB/RIF sensitivity for TB detection.

We included only two studies that used Xpert MTB/RIF G4, the version in current use. We excluded one study of Xpert MTB/RIF G4 (based on concern about the use of duplicate data and discrepant analyses); however, we feel the findings from this study for rifampicin resistance detection are worth mentioning. The Foundation for Innovative Diagnostics (FIND) evaluated the performance of Xpert MTB/RIF G4 using archived sputum specimens from individuals with presumed TB from Germany, Peru, Azerbaijan, Uganda, Cape Town, and South Africa (FIND 2011). Conventional DST for rifampicin resistance was mainly performed by the Lowenstein-Jensen proportion method or MGIT. Genetic sequencing was performed on samples with discordant Xpert MTB/RIF/conventional DST results and these results were used for determination of sensitivity and specificity. The overall sensitivity (rifampicin resistant) was 98.9% (87/88) (95% CI 93.8% to 99.8%) and the overall specificity (rifampicin sensitive) was 99.8% (433/434) (95% CI 98.7% to 100.0%). For Xpert MTB/RIF rifampicin-sensitive/DST-resistant discordants, sequencing of the *rpoB* region was performed in four cases and discordant results resolved in three of these cases; for Xpert MTB/RIF rifampicin-resistant/DST-sensitive discordants, sequencing of the *rpoB* region was performed in nine cases and discordant results resolved in eight of these cases (FIND 2011). In light of these findings, we would expect G4 to have comparable or increased accuracy for rifampicin resistance detection compared with earlier Xpert MTB/RIF versions.

We acknowledge that patient outcomes are clearly important to patients, decision makers, and the wider TB community. Outcomes in addition to diagnostic accuracy, however, could not be systematically addressed, as they would have required a different methodology. Nonetheless, we looked for and summarized two 'time to event' outcomes (time to result and time to treatment initiation) when data were provided in the included studies (Table 5). Xpert MTB/RIF results for TB detection were usually reported within two hours or on the same day, compared with liquid culture results reported in around 16 to 20 days. Studies reporting on time to detection of rifampicin resistance found that, compared with conventional methods, Xpert MTB/RIF greatly decreased the time to diagnosis. However, early detection of rifampicin resistance may not lead to improved patient outcomes if the result is not linked to appropriate treatment, services, and supervision (WHO Xpert MTB/RIF Checklists 2011). Two studies provided information about time to treatment initiation. In Boehme 2011, for smear-negative, culture-positive TB, the median delay in beginning treatment was 56 days (IQR 39 to 81) before Xpert MTB/RIF was introduced, compared with five days (IQR 2 to 8) after Xpert MTB/RIF was introduced. In Van Rie 2013, for smear-negative, culture-positive TB patients with Xpert MTB/RIF positive results, treatment was begun on the same day compared with 13 days for patients diagnosed by other methods. Data regarding delays in switching from the standard regimen for drug-susceptible TB to an appropriate regimen for MDR-TB would also be useful because of the potential harms to patients being treated with the wrong drug regimen. We are aware of several recently completed RCTs in South Africa, Brazil, and India that will give insights on user acceptability, operational performance, and patient-important outcomes (Durovni 2013; Raizada 2013; Theron 2013). These and other studies on patient outcomes will need to be systematically reviewed.

A recent analysis of cost and affordability found that, globally, the use of Xpert MTB/RIF to diagnose MDR-TB would cost less

(US$70 to 90 million per year) than what it would cost to use a combination of conventional diagnostics (US$123 to 191 million per year). Conventional diagnostics may include smear microscopy, chest radiography, culture, and culture-based DST following WHO-recommended algorithms. In addition, using Xpert MTB/RIF to diagnose TB in people living with HIV would also cost less than conventional diagnostics, both globally and in the vast majority of high TB burden countries. However, for almost all countries, the deployment of Xpert MTB/RIF to diagnose TB in all individuals with signs and symptoms of TB would cost more than the use of conventional diagnostics (which may include smear microscopy and follow-up chest radiography for those with smear-negative results) (Pantoja 2013). Several additional cost-effectiveness studies have been published (Abimbola 2012; Andrews 2012; Dowdy 2011; Meyer-Rath 2012; Schnippel 2012; Vassall 2011).

Xpert MTB/RIF has now begun to be rolled out in over 20 countries via UNITAID, with a price drop from $16.86 to $9.98 (US) per cartridge, a price that will remain in effect until 2022 (The Gates Foundation 2012; UNITAID 2012). UNITAID is a global health initiative working to increase access for tests and medicines for HIV/AIDS, TB, and malaria. Since WHO endorsed the use of Xpert MTB/RIF, country-level policy makers have been making decisions about adoption and scale-up. The uptake has been much faster than for any other TB technology recommended by WHO over the last 10 years.

This review represents the most comprehensive review on the diagnostic accuracy of Xpert MTB/RIF and provides evidence that may help countries make decisions about scaling up Xpert MTB/RIF for programmatic management of TB and drug-resistant TB. Although the information in this review will help to inform, other factors such as level of deployment in the health system, cost, and operational considerations (including the ability to maintain an uninterrupted and stable electrical power supply, temperature control, and maintenance of the cartridge modules) will also influence those decisions, as discussed in recent publications (Trébucq 2011; Denkinger 2013).

Summary of main results

We have summarized the main results in the Summary of Findings tables (Summary of findings 1;Summary of findings 2; and Summary of findings 3).

- When used as an initial test replacing smear microscopy, Xpert MTB/RIF detected 89% of TB cases with high specificity (99%).
- When used as an add-on test following smear microscopy, Xpert MTB/RIF detected 67% of TB cases with high specificity (99%).
- Xpert MTB/RIF sensitivity for smear-positive, culture-positive TB was 98%.
- In comparison with smear microscopy, Xpert MTB/RIF increased TB detection among culture-confirmed cases by 23%.
- Xpert MTB/RIF detected 79% of pulmonary TB cases in people infected with HIV and 86% of pulmonary TB cases in people without HIV. However, after adjustment for smear status, there was no evidence of a difference between the HIV-positive and HIV-negative subgroups.
- When used as an initial test replacing phenotypic culture-based DST, Xpert MTB/RIF detected 95% of rifampicin-resistant TB cases with a specificity of 98%.
- The pooled proportion of Xpert MTB/RIF uninterpretable results was very low.

Application of the meta-analysis to a hypothetical cohort

The Summary of findings tables summarize the findings of the review by applying the results to a hypothetical cohort of 1000 individuals thought to have TB or MDR-TB. We present several different scenarios: for Xpert MTB/RIF used as an initial test for TB detection or as an add-on test following microscopy, the prevalence of TB in the setting or patient subgroup varies from 2.5% to 5% to 10%; and for Xpert MTB/RIF for rifampicin resistance detection, the prevalence of rifampicin resistance in the setting varies from 5% to 15% (5% is estimated to be equivalent to the upper limit for rifampicin resistance prevalence in new cases; 15% is estimated to be the lower limit for rifampicin resistance prevalence among previously treated cases). The consequences of false positive results are likely patient anxiety, morbidity from additional testing and unnecessary treatment, and possible delay in further diagnostic evaluation. The consequences of false negative results are an increased risk of patient morbidity and mortality, and continued risk of community transmission of TB.

I. Xpert MTB/RIF for TB detection

A. Xpert MTB/RIF used as an initial test replacing smear microscopy in a population unselected by smear status

TB prevalence of 2.5%: if the pooled estimates for Xpert MTB/RIF are applied to a hypothetical cohort of 1000 patients thought to have TB, where 25 patients actually do have TB, then Xpert MTB/RIF would be expected to miss three cases and falsely diagnose 10 cases (Summary of findings 1).

TB prevalence of 5%: if the pooled estimates for Xpert MTB/RIF are applied to a hypothetical cohort of 1000 patients thought to have TB, where 50 patients actually do have TB, then Xpert MTB/RIF would be expected to miss six cases and falsely diagnose 10 cases (Summary of findings 1).

TB prevalence of 10%; if the pooled estimates for Xpert MTB/RIF are applied to a hypothetical cohort of 1000 patients thought to have TB, where 100 patients actually do have TB, then Xpert MTB/RIF would be expected to miss 11 cases and falsely diagnose nine cases (Summary of findings 1).

If the pooled estimates for Xpert MTB/RIF and smear microscopy are applied to a hypothetical cohort of 1000 patients where 10% of those presenting with symptoms have TB, Xpert MTB/RIF will diagnose 88 cases and miss 12 cases, whereas sputum microscopy will diagnose 65 cases and miss 35 cases (Summary of findings 2)

B. Xpert MTB/RIF used as an add-on test following a negative smear microscopy result

TB prevalence of 2.5%; if the pooled estimates for Xpert MTB/RIF are applied to a hypothetical cohort of 1000 patients thought to have TB, where 25 patients actually do have TB, then Xpert MTB/RIF would be expected to miss eight cases and falsely diagnose 10 cases (Summary of findings 1).

TB prevalence of 5%: if the pooled estimates for Xpert MTB/RIF are applied to a hypothetical cohort of 1000 patients thought to have TB, where 50 patients actually do have TB, then Xpert MTB/RIF would be expected to miss 17 cases and falsely diagnose 10 cases (Summary of findings 1).

TB prevalence of 10%: if the pooled estimates for Xpert MTB/RIF are applied to a hypothetical cohort of 1000 patients thought to have TB, where 100 patients actually do have TB, then Xpert MTB/RIF would be expected to miss 33 cases and falsely diagnose nine cases (Summary of findings 1).

II. Xpert MTB/RIF for rifampicin resistance detection

A. Xpert MTB/RIF used as an initial test for rifampicin resistance replacing conventional DST as the initial test

If the pooled estimates for Xpert MTB/RIF are applied to a hypothetical cohort of 1000 individuals where 15% of those presenting with symptoms are rifampicin resistant, Xpert MTB/RIF would correctly identify 143 individuals as rifampicin resistant and miss eight cases and 833 individuals as rifampicin susceptible and wrongly identify 17 individuals as resistant. In comparison, where 5% of those presenting with symptoms are rifampicin resistant, Xpert MTB/RIF would correctly identify 48 individuals as rifampicin resistant and miss three cases and correctly identify 931 individuals as rifampicin susceptible and wrongly identify 19 individuals as resistant (Summary of findings 3).

Strengths and weaknesses of the review

The findings in this review are based on comprehensive searching, strict inclusion criteria, and standardized data extraction. The strength of our review is that it enables an assessment of the diagnostic accuracy of Xpert MTB/RIF for detection of TB when Xpert MTB/RIF is used as a replacement test for smear microscopy or as an add-on test following smear microscopy. In addition, the review allows a determination of the accuracy of Xpert MTB/RIF for detection of rifampicin resistance when Xpert MTB/RIF is used as an initial test replacing conventional DST.

Completeness of evidence

This data set involved comprehensive searching and correspondence with experts in the field and the test manufacturer to identify additional studies, as well as repeated correspondence with study authors to obtain additional data and information that was missing from the papers. The search strategy included studies published in all languages. However, we acknowledge that we may have missed some studies despite the comprehensive search. Lastly, the evidence in this review is mostly derived from high TB incidence countries and should be carefully extrapolated to low incidence settings.

Accuracy of the reference standards used

Culture is regarded as the best available reference standard for active TB disease and was the reference standard for TB in this review. Phenotypic culture-based DST methods using WHO-recommended critical concentrations were the reference standards for rifampicin resistance (WHO Policy DST 2008). Concerning the latter, several studies have raised concerns about rapid DST methods, in particular automated MGIT 960, for rifampicin using the recommended critical concentrations. Van Deun 2009 reported that BACTEC 460 and MGIT 960 missed certain strains associated with low-level rifampicin resistance. Furthermore, using Xpert MTB/RIF and gene sequencing, Williamson 2012a identified four patients (three with clinical information available) whose TB isolates contained mutations to the *rpoB* gene but appeared to be rifampicin susceptible using MGIT 960 (36). In this study, 2/49 (4.1%) patients whose isolates did not have apparent *rpoB* gene mutations, experienced treatment failure compared with 3/3 (100%) patients whose isolates did have *rpoB* gene mutations and were deemed rifampicin susceptible with phenotypic methods (Williamson 2012a). Recently, in a study involving retreatment patients, Van Deun and colleagues found that disputed *rpoB* mutations conferring low-grade resistance were often missed by rapid phenotypic DST, particularly with the MGIT 960 system, but to a minor extent also by conventional slow DST. The authors suggested this may be the reason for the perceived insufficient specificity of molecular DST for rifampicin (Van Deun 2013). In light of these findings, it is unclear whether and to what extent Xpert MTB/RIF might out-perform phenotypic DST methods for rifampicin resistance. Specifically, the determination of the specificity of a molecular DST method based on phenotypic DST alone may underestimate the specificity of a molecular DST.

Quality and quality of reporting of the included studies

The majority of studies used consecutive selection of participants and interpreted the reference standard results without knowledge

of Xpert MTB/RIF results. Xpert MTB/RIF results are generated automatically, without requiring subjective interpretation. In general, studies were fairly well reported, though we corresponded with almost all authors for additional data and missing information. We encourage authors of future studies to follow the recommendations in the STARD statement to improve the quality of reporting (Bossuyt 2003).

Completeness and relevance of the review

We noted that most studies performed Xpert MTB/RIF in intermediate-level or peripheral-level laboratories, which are settings that matched the review question. This review included studies using all four generations of Xpert MTB/RIF (G1, G2, G3, G4 cartridges). G4, which is used with software version 4.0 or higher, is now included in all Xpert MTB/RIF kits. This review did not address the use of Xpert MTB/RIF in children or in non-respiratory specimens for the diagnosis of extrapulmonary TB.

Applicability of findings to the review question

We found Xpert MTB/RIF to be sensitive and specific for TB detection and rifampicin resistance detection with relatively few false-positive and false-negative results. The consequences of false-positive results are likely patient anxiety, morbidity from additional and unnecessary testing and, particularly in the case of second-line anti-TB drugs, costly treatment and possible delay in further diagnostic evaluation. The consequences of false-negative results are an increased risk of patient morbidity and mortality, and continued risk of community transmission of TB. The majority of studies evaluated the accuracy of Xpert MTB/RIF in sputum specimens submitted by patients thought to have TB, and conducted the test outside of central laboratories. Although the patient characteristics and settings matched our review question, as studies were carried out under research conditions, it is possible that the accuracy of Xpert MTB/RIF may be lower in routine practice settings. In studies assessing the impact of Xpert MTB/RIF on patient outcomes, Xpert MTB/RIF results for TB detection were reported more rapidly than liquid culture results, and Xpert MTB/RIF results for rifampicin resistance detection were reported much faster than culture-based methods.

AUTHORS' CONCLUSIONS

Implications for practice

In adults thought to have TB, with or without HIV infection, Xpert MTB/RIF is sensitive and specific. In comparison with smear microscopy, this test substantially increases TB detection among culture-confirmed cases. Xpert MTB/RIF has higher sensitivity for TB detection in smear-positive patients than smear-negative patients. Nonetheless, it may also be valuable as an add-on test following smear microscopy in patients who have previously been found to be smear-negative. For detection of rifampicin resistance, in adults thought to have MDR-TB, Xpert MTB/RIF provides accurate results and can allow rapid initiation of MDR-TB treatment, pending results from conventional culture and DST. The ongoing use of Xpert MTB/RIF in TB programmes in high TB burden settings, as well as its use in primary care clinics where the test provides the opportunity to begin treatment promptly, will contribute evidence on whether its use leads to improvements in patient health.

Implications for research

Future studies should assess the diagnostic accuracy of Xpert MTB/RIF in peripheral-level laboratories and clinical settings, such as primary health facilities, TB screening centres, and antiretroviral clinics, especially settings where the test is performed at the point of care. Systematic reviews have been performed on Xpert MTB/RIF for the diagnosis of extrapulmonary TB and paediatric TB and the findings described in the updated WHO policy statement on the use of Xpert MTB/RIF (WHO Xpert MTB/RIF Policy Update 2013). Future systematic reviews should summarize the growing body of evidence on patient and public health, cost, and cost effectiveness.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Al-Ateah 2012

Study characteristics			
Patient sampling	Cross-sectional design with consecutive enrolment of participants, prospective data collection		
Patient characteristics and setting	Presenting signs and symptoms: Not stated Age: Not stated Sex, female: 46.2% HIV infection: 0.6% History of TB: Not stated Sample size: 172 Clinical setting: Laboratory-based evaluation of respiratory specimens Laboratory level: Intermediate Country: Saudi Arabia World Bank Income Classification: High-income TB incidence rate: 17 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 1.8% (Source: Nationwide survey 2010) and among retreatment cases = 16% (Source: Nationwide survey 2010) Proportion of TB cases in the study: 25.6%		
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Processed Xpert MTB/RIF version: Not stated		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960		
Flow and timing			
Comparative			
Notes	The majority of specimens were obtained from bronchoalveolar lavage		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**High**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Were all patients included in the analysis?	Yes		
		Low	

Balcells 2012

Study characteristics			
Patient sampling	Cross-sectional design with consecutive enrolment of patients, prospective data collection		
Patient characteristics and setting	Presenting signs and symptoms: Patients who fulfilled at least one of the following criteria: cough (> 10 days), bloody sputum, pneumonia unresponsive to previous antibiotics, fever (> 10 days), abnormal CXR or weight loss Age: Mean 37.4 years (range 19 to 65) Sex, female: 20.6% HIV infection: 100% History of TB: 11.8% Sample size: 160 Clinical setting: Five hospitals and their respective HIV clinics Laboratory level: Intermediate Country: Chile World Bank Income Classification: Middle-income TB incidence rate: 18 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 0.7% (Source: Nationwide survey 2001) and among retreatment cases = 3.2% (Source: Nationwide surveillance 2011) Proportion of TB cases in the study: 7.5%		
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Processed Xpert MTB/RIF version: 2 and 3		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: Proportion method on Löwenstein-Jensen media		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Barnard 2012

Study characteristics	
Patient sampling	Cross-sectional design with consecutive enrolment of patients, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: Not stated Age: Predominantly adult, median age 41 Sex, female: 43.6% HIV infection: Not stated History of TB: 100% Sample size: 68 Clinical setting: Laboratory-based evaluation of clinical specimens from previously treated patients Laboratory level: Intermediate Country: South Africa, Cape Town World Bank Income Classification: Middle-income TB incidence rate: per 993 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 0.9% (Source: Survey in Western Cape Province, 2002) and among retreatment cases = 4.0% (Source: Survey in Western Cape Province, 2002) Proportion of TB cases in the study: 76.5%
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Processed Xpert MTB/RIF version: 3
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: MGIT 960
Flow and timing	
Comparative	
Notes	Fifteen patients submitted specimens for treatment monitoring, not diagnosis; three patients were 5, 7, and 10 years of age; all other patients were 16 years of age or older; according to GenoType MTBDRplus (v1.0) assay as the reference standard, Xpert MTB/RIF sensitivity and specificity for rifampicin resistance detection were 100% (based on three rifampicin resistant samples; 33 rifampicin susceptible samples)

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			

Barnard 2012 (*Continued*)

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Boehme 2010a

Study characteristics	
Patient sampling	Prospective study with consecutive enrolment of participants; site in a multicentre study
Patient characteristics and setting	Presenting signs and symptoms: Persistent productive cough for ≥ two weeks Age: Median 37 years; range 20 to 69 years Sex, female: 0% HIV infection: 4.7% History of TB: 54.6% Sample size: 216 Clinical setting: Special treatment facility for prisoners, high MDR-TB setting Laboratory level: Central Country: Azerbaijan World Bank Income Classification: Middle-income TB incidence rate: 113 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 22% (Source: survey in Baku City, 2007) and among retreatment cases = 56% (Source: survey in Baku City, 2007) Proportion of TB cases in study centre: 68.1%
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 1
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: Proportion method on Löwenstein-Jensen media
Flow and timing	
Comparative	

Notes	Women were not included, but otherwise considered representative spectrum Data for one specimen per patient were provided by the study author		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
		Low	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		

Boehme 2010a (*Continued*)

		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Boehme 2010b

Study characteristics	
Patient sampling	Prospective study with consecutive enrolment of participants; site in a multicentre study
Patient characteristics and setting	Presenting signs and symptoms: Persistent productive cough for ≥ two weeks Age: Median 31 years; range 18 to 79 years Sex, female: 43.3% HIV infection: 1.7% History of TB: 23.7% Sample size: 310 Clinical setting: Primary health care DOTS (directly observed treatment, short-course) centres in shanty towns Laboratory level: Intermediate Country: Peru World Bank Income Classification: Middle-income TB incidence rate: 101 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 5.3% (Source: Nationwide survey 2006) and among retreatment cases = 24% (Source: Nationwide survey 2006) Proportion of TB cases in study centre: 67.4%
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 1
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: Proportion method on Löwenstein-Jensen media

Flow and timing			
Comparative			
Notes	Data for one specimen per patient were provided by the study author		

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without	Yes		

Boehme 2010b (*Continued*)

knowledge of the results of the index test?			
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Boehme 2010c

Study characteristics	
Patient sampling	Prospective study with consecutive enrolment of participants; site in a multicentre study
Patient characteristics and setting	Presenting signs and symptoms: Persistent productive cough for ≥ two weeks Age: Median 36 years; range 18 to 80 years Sex, female: 34.1% HIV infection: 76.1% History of TB: 43.0% Sample size: 332 Clinical setting: Clinic, high HIV setting Laboratory level: Intermediate Country: South Africa, Cape Town World Bank Income Classification: Middle-income TB incidence rate: per 993 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 0.9% (Source: Survey in Western Cape Province, 2002) and among retreatment cases = 4.0% (Source: Survey in Western Cape Province, 2002) Proportion of TB cases in study centre: 44.0%
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 1
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MGIT 960 Target condition: Rfiampicin resistance

Boehme 2010c (*Continued*)

	Reference standard for rifampicin resistance: MGIT 960		
Flow and timing			
Comparative			
Notes	Data for one specimen per patient were provided by the study author		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		

Boehme 2010c (*Continued*)

Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Boehme 2010d

Study characteristics	
Patient sampling	Prospective study with consecutive enrolment of participants; site in a multicentre study
Patient characteristics and setting	Presenting signs and symptoms: Persistent productive cough for ≥ two weeks Age: Median 32 years; range 18 to 68 years Sex, female: 59.4% HIV infection: 71.4% History of TB: 45.1% Sample size: 261 Clinical setting: TB clinics, high HIV setting Laboratory level: Central Country: South Africa, Durban World Bank Income Classification: Middle-income TB incidence rate: 993 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 1.7% (Source: Survey in Kwazulu-Natal Province, 2002) and among retreatment cases = 7.7% (Source: Survey in Kwazulu-Natal Province, 2002) Proportion of TB cases in study centre: 16.5%
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 1

Boehme 2010d (*Continued*)

Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Middlebrook 7H11 culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: Proportion method on Löwenstein-Jensen media		
Flow and timing			
Comparative			
Notes	Data for one specimen per patient were provided by the study author		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of	Yes		

Boehme 2010d (*Continued*)

the results of the index test?			
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		Low	

Boehme 2010e

Study characteristics	
Patient sampling	Prospective study with consecutive enrolment of participants; site in a multicentre study
Patient characteristics and setting	Presenting signs and symptoms: Persistent productive cough for ≥ two weeks Age: Median 30 years; range 17 to 88 years Sex, female: 39.1% HIV infection: 4.4% History of TB: 75.2% Sample size: 222 Clinical setting: Tertiary hospital, high MDR-TB setting Laboratory level: Intermediate Country: India World Bank Income Classification: Middle-income TB incidence rate: 181 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 2.1% (Source: Survey in Andhra Pradesh, 2009) and among retreatment cases = 12% (Source: Survey in Andhra Pradesh, 2009) Proportion of TB cases in study centre: 84.2%
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 1

Boehme 2010e (*Continued*)

Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960		
Flow and timing			
Comparative			
Notes	Data for one specimen per patient were provided by the study author		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of	Yes		

Boehme 2010e (*Continued*)

the results of the index test?			
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		Low	

Boehme 2011a

Study characteristics	
Patient sampling	Prospective study with consecutive enrolment of participants; site in a multicentre study
Patient characteristics and setting	Presenting signs and symptoms: Cough lasting at least two weeks Age: Median 36 years; IQR 30 to 44 years Sex, female: < 1% HIV infection: < 1% History of TB: Not stated Sample size: 536 for detection of MTB; 211 for detection of rifampicin resistance Clinical setting: MDR-TB screening facility Laboratory level: Intermediate Country: Azerbaijan World Bank Income Classification: Middle-income TB incidence rate: 113 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 22% (Source: survey in Baku City, 2007) and among retreatment cases = 56% (Source: survey in Baku City, 2007) Proportion of TB cases in study centre: 42.7%
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 3

Boehme 2011a (*Continued*)

Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960		
Flow and timing			
Comparative			
Notes	Follow-up reported for all sites combined: 24/153 patients with culture-negative, clinically diagnosed TB had positive results on MTB/RIF testing. 20/24 patients had follow-up, and all 20 improved on TB treatment		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Boehme 2011a (*Continued*)

Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Boehme 2011b

Study characteristics	
Patient sampling	Prospective study with consecutive enrolment of participants; site in a multicentre study
Patient characteristics and setting	Presenting signs and symptoms: Cough lasting at least two weeks Age: Median 37 years; IQR 26 to 53 years Sex, female: 49% HIV infection: < 1% History of TB: Not stated Sample size: 1005 for detection of TB; 185 for detection of rifampicin resistance Clinical setting: Two health centres and one district hospital Laboratory level: Intermediate Country: Peru World Bank Income Classification: Middle-income TB incidence rate: 101 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 5.3% and among retreatment cases = 23.6% (Source: Nationwide survey, 2006) Proportion of TB cases in study centre: 17.6%

Boehme 2011b (*Continued*)

Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 3		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960		
Flow and timing			
Comparative			
Notes	Follow-up was reported for all sites combined, see Boehme 2011a		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			

Boehme 2011b (*Continued*)

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Boehme 2011c

Study characteristics	
Patient sampling	Prospective study with consecutive enrolment of participants; site in a multicentre study
Patient characteristics and setting	Presenting signs and symptoms: Cough lasting at least two weeks Age: Median 36 years; IQR 29 to 46 years Sex, female: 49% HIV infection: 38% History of TB: Not stated Sample size: 904 for detection of TB; 188 for detection of rifampicin resistance Clinical setting: One health centre and one provincial hospital Laboratory level: Intermediate Country: South Africa, Cape Town World Bank Income Classification: Middle-income TB incidence rate: 993 per 100,000

	MDR-TB prevalence: Percent MDR-TB among new TB cases = 0.9% and among retreatment cases = 4.0% (Source: Survey in Western Cape Province, 2002) Proportion of TB cases in study centre: 25.8%		
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 3		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960 and MTBDRplus		
Flow and timing			
Comparative			
Notes	Follow-up was reported for all sites combined, see Boehme 2011a MTBDRplus was done on culture isolates for smear-negative sputum		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**

Boehme 2011c (*Continued*)

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		Low	

Boehme 2011d

Study characteristics	
Patient sampling	Prospective study with consecutive enrolment of participants; site in a multicentre study
Patient characteristics and setting	Presenting signs and symptoms: Cough lasting at least two weeks Age: Median 32 years; IQR 26 to 38 years Sex, female: < 46% HIV infection: < 68% History of TB: Not stated Sample size: 289 for detection of TB; 116 for detection of rifampicin resistance Clinical setting: Emergency unit of referral hospital Laboratory level: Intermediate Country: Uganda

	World Bank Income Classification: Low-income TB incidence rate: 193 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 1.4% (Source: Nationwide survey, 2011) and among retreatment cases = 12% (Source: Nationwide survey, 2011) Proportion of TB cases in the study centre: 50.2%
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 3
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: Proportion method on Löwenstein-Jensen media and line probe assay
Flow and timing	
Comparative	
Notes	Follow-up was reported for all sites combined, see Boehme 2011a Line-probe assay and, for 10% of culture positive patients (every tenth patient), Löwenstein-Jensen proportion was performed on MGIT isolates (except when only positive on Löwenstein-Jensen)

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Boehme 2011d (*Continued*)

If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		Low	

Boehme 2011e

Study characteristics	
Patient sampling	Prospective study with consecutive enrolment of participants; site in a multicentre study
Patient characteristics and setting	Presenting signs and symptoms: Cough lasting at least two weeks Age: Median 45 years; IQR 32 to 58 years Sex, female: 30% HIV infection: 4% History of TB: Not stated

	Sample size: 788 for detection of TB; 103 for detection of rifampicin resistance Clinical setting: Health centre Laboratory level: Intermediate Country: India World Bank Income Classification: Middle-income TB incidence rate: 181 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 2.1% (Source: Survey in Andhra Pradesh, 2009) and among retreatment cases = 12% (Source: Survey in Andhra Pradesh, 2009) Proportion of TB cases in the study centre: 12.8%
Index tests	Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 3
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture Target condition: Rifampicin resistance Reference standard for rifampicin resistance: Proportion method on Löwenstein-Jensen media
Flow and timing	
Comparative	
Notes	Follow-up was reported for all sites combined, see Boehme 2011a

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Boehme 2011e (*Continued*)

If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Boehme 2011f

Study characteristics	
Patient sampling	Prospective study with consecutive enrolment of participants; site in a multicentre study
Patient characteristics and setting	Presenting signs and symptoms: Cough lasting at least two weeks Age: Median 47 years; IQR 34 to 58 years Sex, female: 36% HIV infection: < 1% History of TB: Not stated

	Sample size: 387 for detection of TB; 257 for detection of rifampicin resistance Clinical setting: MDR-TB screening facility Laboratory level: Intermediate Country: Philippines World Bank Income Classification: Middle-income TB incidence rate: 270 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 4% (Source: Nationwide survey, 2004) and among retreatment cases = 21% (Source: Nationwide survey, 2004) Proportion of TB cases in the study centre: 38.2%		
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 3		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Ogawa culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: Proportion method on Löwenstein-Jensen media		
Flow and timing			
Comparative			
Notes	Follow-up was reported for all sites combined, see Boehme 2011a		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Boehme 2011f (*Continued*)

If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		
		Low	

Bowles 2011

Study characteristics	
Patient sampling	Prospective and retrospective study with enrolment of participants by convenience
Patient characteristics and setting	Presenting signs and symptoms: Not reported Age: Not stated Sex, female: Not stated HIV infection: Not stated History of TB: Not stated

	Sample size: 89 Clinical setting: Laboratory-based evaluation of respiratory specimens (predominantly sputum specimens) from a TB reference clinic Laboratory level: Central Country: Netherlands World Bank Income Classification: High-income TB incidence rate: 6.8 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 1.7% and among retreatment cases = 4.5% (Source: Nationwide surveillance, 2011) Proportion of TB cases in the study: 71.9%		
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: 26 fresh and 63 frozen (previously stored) samples Specimen Preparation: Unprocessed Xpert MTB/RIF version: 1		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960		
Flow and timing			
Comparative			
Notes	Sample included two extrapulmonary specimens (one pleural fluid and one gastric aspirate) One patient whose sample was smear and culture-negative was culture-positive on a sample 11 days later		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	**Unclear**
DOMAIN 2: Index Test All tests			

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
		Unclear	

Carriquiry 2012

Study characteristics			
Patient sampling	Cross-sectional design with consecutive enrolment of patients, prospective data collection		
Patient characteristics and setting	Presenting signs and symptoms: Cough for greater than 10 days with abnormal chest X-ray and at least one of the following symptoms: fever, fatigue, night sweats, haemoptysis, chest pain, or weight loss Age: Median 35 years (IQR 29 to 42) Sex, female: 27.5% HIV infection: 100% History of TB: 57.3% Sample size: 131 Clinical setting: Two tertiary hospitals Laboratory level: Intermediate Country: Peru World Bank Income Classification: Middle-income TB incidence rate: 101 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 5.3% (Source: Nationwide survey 2006) and among retreatment cases = 24% (Source: Nationwide survey 2006) Proportion of TB cases in the study: 34.4%		
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 2		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: Proportion method on Löwenstein-Jensen media		
Flow and timing			
Comparative			
Notes			

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Ciftci 2011

Study characteristics			
Patient sampling	Prospective study; the sampling method was unclear		
Patient characteristics and setting	Presenting signs and symptoms: Symptoms suggestive of TB Age: Not stated Sex, female: Not stated HIV infection: Not stated History of TB: Not stated Sample size: 85 Clinical setting: Laboratory-based evaluation of respiratory specimens (predominantly sputum) at a university hospital Laboratory level: Intermediate Country: Turkey World Bank Income Classification: Middle-income TB incidence rate: 24 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 0.9% (Source: Survey in Ankara City 2011) and among retreatment cases = 38% (Source: Survey in Ankara City 2011) Proportion of TB cases in the study: 29.4%		
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: Fresh Specimen Preparation: Unprocessed Xpert MTB/RIF version: 1		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: BACTEC 460 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: BACTEC 460		
Flow and timing			
Comparative			
Notes	Paper was written in Turkish: sample included 10 extrapulmonary specimens (five pleural fluid and five urine samples); no patients were found to have rifampicin resistance		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		

Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
		Unclear	

Friedrich 2011

Study characteristics			
Patient sampling	Prospective study with consecutive enrolment of participants		
Patient characteristics and setting	Cross-sectional design with consecutive enrolment of participants, prospective data collection Presenting signs and symptoms: Patients recently diagnosed with smear-positive first time TB, untreated Age: Eligible aged 18 to 65 years Sex, female: Not stated HIV infection: Not stated History of TB: Not stated Sample size: 126 Clinical setting: Two medical centres Laboratory level: Intermediate Country: South Africa, Cape Town World Bank Income Classification: Middle-income TB incidence rate: 993 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 0.9% (Source: Survey in Western Cape Province, 2002) and among retreatment cases = 4.0% (Source: Survey in Western Cape Province, 2002) Proportion of TB cases in the study: 100.0%		
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: Fresh Specimen Preparation: Processed Xpert MTB/RIF version: 2 and 4		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960		
Flow and timing			
Comparative			
Notes	The aim of this study was to assess NAATs for selecting patients for clinical trials of anti-TB medication. Patients with severe co-morbidities were excluded. This study was used only for determination of sensitivity because all enrolled patients were predetermined to have TB disease		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
		High	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Friedrich 2011 (*Continued*)

Were all patients included in the analysis?	Yes		
		Low	

Hanif 2011

Study characteristics			
Patient sampling	Prospective study with consecutive enrolment of participants		
Patient characteristics and setting	Presenting signs and symptoms: Presumed TB based on presence of cough and radiographic findings Age: Range 20 to 57 years old Sex, female: Not stated HIV infection: Not stated History of TB: Not stated Sample size: 206 Clinical setting: Laboratory-based evaluation of respiratory specimens (predominantly sputum) at a university hospital Laboratory level: Central Country: Kuwait World Bank Income Classification: High-income TB incidence rate: 36 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 0% and among retreatment cases = 12% (Source: Nationwide surveillance, 2011) Proportion of TB cases in the study: 29.1%		
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: Fresh Specimen Preparation: Unprocessed Xpert MTB/RIF version: 1		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: BACTEC 460		
Flow and timing			
Comparative			
Notes	No patients were found to have rifampicin resistance		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**

Hanif 2011 (*Continued*)

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	No		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		High	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Hanif 2011 (*Continued*)

Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		Low	

Hanrahan 2013

Study characteristics	
Patient sampling	Cross-sectional design with consecutive enrolment of patients, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: Prolonged (> two weeks) cough and/or other TB symptoms Age: 18 and older Sex, female: Not stated HIV infection: Not stated History of TB: Not stated Sample size: 551 Clinical setting: Primary care clinic Laboratory level: Peripheral Country: South Africa, Johannesburg World Bank Income Classification: Middle-income TB incidence rate: 993 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 1.4% (Source: Survey in Gauteng province, 2002) and among retreatment cases = 5.5% (Source: Survey in Gauteng province, 2002) Proportion of TB cases in the study: 11.6%
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 3
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960
Flow and timing	
Comparative	
Notes	
Methodological quality	

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			

Hanrahan 2013 (*Continued*)

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Helb 2010

Study characteristics	
Patient sampling	Retrospective study with consecutive enrolment of participants
Patient characteristics and setting	Presenting signs and symptoms: Cough lasting at least two weeks Age: Median 34 years; range 18 to 76 years Sex, female: 30.8% HIV infection: 0.9% History of TB: 1.9% Sample size: 107 Clinical setting: TB hospital Laboratory level: Intermediate Country: Vietnam World Bank Income Classification: Middle-income TB incidence rate: 199 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 2.7% (Source: Nationwide survey, 2006) and among retreatment cases = 19% (Source: Nationwide survey, 2006) Proportion of TB cases in the study: 76.6%
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: Frozen Specimen Preparation: Unprocessed Xpert MTB/RIF version: 1
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard: Löwenstein-Jensen culture and MGIT 960
Flow and timing	
Comparative	
Notes	Rifampicin resistance data were not reported
Methodological quality	

Helb 2010 (*Continued*)

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			

Helb 2010 (*Continued*)

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
		Unclear	

Ioannidis 2011

Study characteristics	
Patient sampling	Prospective and retrospective study with enrolment of participants by convenience
Patient characteristics and setting	Presenting signs and symptoms: High suspicion of TB in patients found to be predominantly smear negative by microscopy examination Age: Not stated Sex, female: Not stated HIV infection: Not stated History of TB: Not stated Sample size: 66 Clinical setting: Laboratory-based evaluation in routine hospital setting Laboratory level: Central Country: Greece World Bank Income Classification: High-income TB incidence rate: 3.8 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 0.9% (Source: Nationwide surveillance, 2010) and among retreatment cases = 6.7% (Source: Nationwide surveillance, 2010) Proportion of TB cases in the study: 48.0%
Index tests	Index: Xpert MTB/RIF assay Condition: Fresh Preparation: Processed Xpert MTB/RIF version: 2
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: Proportion method on Löwenstein-Jensen media
Flow and timing	
Comparative	

Ioannidis 2011 (*Continued*)

Notes	Specimens were predominantly smear-negative		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**

Ioannidis 2011 (*Continued*)

DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Kurbatova 2013

Study characteristics	
Patient sampling	Cross-sectional design with consecutive enrolment of patients, prospective data collection
Patient characteristics and setting	Presenting signs and symptoms: Presumptive or recently diagnosed TB Age: Not stated Sex, female: Not stated HIV infection: estimated < 5 % History of TB: Not stated Sample size: 238 Clinical setting: Laboratory-based evaluation Laboratory level: Central and intermediate Country: Russia World Bank Income Classification: Middle-income TB incidence rate: 97 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 20% (Source: Surveillance in 20 Oblasts 2010) and among retreatment cases = 46% (Source: Surveillance in 20 Oblasts 2008) Proportion of TB cases in the study: 46.9%
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 4
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960
Flow and timing	
Comparative	

Notes	Fresh, unconcentrated sputum was initially homogenized using a vortex with glass beads		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**

Kurbatova 2013 (*Continued*)

DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Lawn 2011

Study characteristics	
Patient sampling	Prospective study with consecutive enrolment of participants
Patient characteristics and setting	Presenting signs and symptoms: HIV-infected patients with advanced immunodeficiency; the majority of patients had one or more of the following TB symptoms: current cough, fever, night sweats, or weight loss Age: Median 34 years; IQR 28 to 41 years Sex, female: 65.4% HIV infection: 100% History of TB: 26.5% Sample size: 394 Clinical setting: HIV anti-retroviral clinic; all patients were screened for TB Laboratory level: Intermediate Country: South Africa, Cape Town World Bank Income Classification: Middle-income TB incidence rate: 993 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 0.9% (Source: Survey in Western Cape Province, 2002) and among retreatment cases = 4.0% (Source: Survey in Western Cape Province, 2002) Proportion of TB cases in the study: 18.3%
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: Fresh Specimen Preparation: Processed Xpert MTB/RIF version: Not stated
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960

Flow and timing			
Comparative			
Notes	This study evaluated the use of Xpert to screen HIV-infected patients with advanced immunodeficiency enrolling in antiretroviral therapy services regardless of symptoms, although the majority of patients in the study had TB symptoms. Of three patients with apparent false-positive Xpert MTB/RIF results, on follow-up, two patients had overt pulmonary and systemic symptoms suggestive of TB and improved on anti-TB treatment. The third patient was lost to follow-up Median CD4 cell count, 171 cells/ml; IQR 102 to 236		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**High**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of	Yes		

Lawn 2011 (*Continued*)

the results of the index test?			
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Malbruny 2011

Study characteristics	
Patient sampling	Prospective and retrospective study with enrolment of participants by convenience
Patient characteristics and setting	Presenting signs and symptoms: Clinical symptoms suggestive of TB Age: Median 52 years Sex, female: 40.2% HIV infection: Not stated History of TB: Not stated Sample size: 58 Clinical setting: Laboratory-based evaluation of respiratory specimens (predominantly bronchial aspirates) at a university hospital Laboratory level: Intermediate Country: France World Bank Income Classification: High-income TB incidence rate: 4.3 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 1.0% (Source: Nationwide surveillance, 2009) and among retreatment cases = 13% (Source: Nationwide surveillance, 2009) Proportion of TB cases in the study: 20.7%
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: Fresh and frozen Specimen Preparation: Processed

	Xpert MTB/RIF version: 1 and 2		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Solid culture, type unspecified, and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960		
Flow and timing			
Comparative			
Notes	31/58 (53.4%) of samples were bronchial aspirates One rifampicin-resistant isolate was identified		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	**High**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Marlowe 2011

Study characteristics	
Patient sampling	Prospective and retrospective study with selection of specimens by convenience at two sites and consecutive selection of smear-positive specimens at one site
Patient characteristics and setting	Presenting signs and symptoms: Not reported Age: Not stated Sex, female: Not stated HIV infection: Not stated History of TB: Not stated Sample size: 216 Clinical setting: Laboratory-based evaluation of respiratory samples Laboratory level: Central (one laboratory) and intermediate (two laboratories) Country: USA World Bank Income Classification: High income TB incidence rate: 3.9 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 1.4% (Source: Nationwide surveillance, 2011) and among retreatment cases = 7.6% (Source: Nationwide surveillance, 2011) Proportion of TB cases in the study: 60.2%

Marlowe 2011 (*Continued*)

Index tests	Index: Xpert MTB/RIF assay Condition: Fresh and frozen Preparation: Processed Xpert MTB/RIF version: Not stated		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture, Middlebrook 7H11 culture, and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: phenotypic drug susceptibility testing with agar-based solid media and MGIT 960		
Flow and timing			
Comparative			
Notes	Unit of analysis was specimen Different reference standards were used at each of the three sites		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			

Marlowe 2011 (*Continued*)

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		Low	

Miller 2011

Study characteristics	
Patient sampling	Retrospective study; with enrolment of participants by convenience
Patient characteristics and setting	Presenting signs and symptoms: Not reported Age: Data provided for patients with pulmonary and extrapulmonary combined; 95% of patients were 15 years and older Sex, female: Not stated HIV infection: Not stated History of TB: Not stated Sample size: 89 pulmonary specimens (in addition, study included 23 extrapulmonary specimens) Clinical setting: Laboratory-based evaluation of clinical specimens at a university hospital Laboratory level: Intermediate Country: USA World Bank Income Classification: High income

Miller 2011 (*Continued*)

	TB incidence rate: 3.9 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 1.4% (Source: Nationwide surveillance, 2011) and among retreatment cases = 7.6% (Source: Nationwide surveillance, 2011) Proportion of TB cases in the study**:** 32.6%		
Index tests	Index: Xpert MTB/RIF assay Condition: Frozen Preparation: Processed Xpert MTB/RIF version: Not stated		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960		
Flow and timing			
Comparative			
Notes	Of specimens tested, four were positive by Xpert MTB/RIF for rifampicin resistance; three were positive by the reference standard		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Miller 2011 (*Continued*)

		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Moure 2011

Study characteristics	
Patient sampling	Retrospective study with enrolment of participants by convenience
Patient characteristics and setting	Presenting signs and symptoms: Patients found to be smear negative by microscopy examination Age: All patients were 15 years of age or older Sex, female: Not stated HIV infection: Not stated History of TB: Not stated Sample size: 107 Clinical setting: Laboratory-based evaluation of clinical specimens at a university hospital Laboratory level: Intermediate

	Country: Spain World Bank Income Classification: High income TB incidence rate: 15 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 0.2% (Source: Survey in Galicia region, 2005) and among retreatment cases = 1.5% (Source: Survey in Galicia region, 2005) Proportion of TB cases in the study: 72.9%
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: Frozen Specimen Preparation: Processed Xpert MTB/RIF version: 1
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Lowenstein-Jensen culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: Bactec 460
Flow and timing	
Comparative	
Notes	Sample set included one pulmonary biopsy specimen Of 85 pulmonary and extrapulmonary specimens tested, six were positive by Xpert MTB/RIF for rifampicin resistance, and seven specimens were positive by the reference standard

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		High	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Rachow 2011

Study characteristics	
Patient sampling	Retrospective study with consecutive enrolment of participants
Patient characteristics and setting	Presenting signs and symptoms: Presumed pulmonary TB based on clinical and radiographic findings Age: Mean 39 years (SD = 13.8) Sex, female: 51.7% HIV infection: 58.9% History of TB: Not stated

	Sample size: 172 Clinical setting: Referral hospital, high HIV setting Laboratory level: Central Country: United Republic of Tanzania World Bank Income Classification: Low-income TB incidence rate: 169 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 1.1% (Source: Nationwide survey, 2007) and among retreatment cases = 0% (Source: Nationwide survey, 2007) Proportion of TB cases in the study: 40.1%
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: Frozen Specimen Preparation: Unprocessed Xpert MTB/RIF version: 1
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960
Flow and timing	
Comparative	
Notes	Patients were followed for a period of 56 days. Among 77 patients classified as smear negative, culture negative 'clinical TB', Xpert MTB/RIF was positive in seven (9.1%) patients No patients were found to have rifampicin resistance

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test All tests			

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
		Unclear	

Safianowska 2012

Study characteristics			
Patient sampling	Cross-sectional design with consecutive enrolment of patients, prospective data collection		
Patient characteristics and setting	Presenting signs and symptoms: Patients presumed to have TB Age: Mean 61 years; range 20 to 97 years Sex, female: 36.6% HIV infection: 0% History of TB: Not stated Sample size: 145 Clinical setting: Laboratory-based evaluation Laboratory level: Intermediate Country: Poland World Bank Income Classification: High-income TB incidence rate: 23 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 0.5% (Source: Nationwide surveillance, 2011) and among retreatment cases = 3.5% (Source: Nationwide surveillance, 2011) Proportion of TB cases in the study: 11.8%		
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: Fresh Specimen Preparation: Processed Xpert MTB/RIF version: 1 and 2		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture Target condition: Rifampicin resistance Reference standard for rifampicin resistance: Löwenstein-Jensen media, method not specified		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Scott 2011

Study characteristics			
Patient sampling	Prospective study with consecutive enrolment of participants		
Patient characteristics and setting	Presenting signs and symptoms: Patients presumed to have TB, presenting with cough, fever, night sweats, and/or weight loss Age: Mean 32 years; range 19 to 75 years Sex, female: 41.1% HIV infection: 69.0% History of TB: Not stated Sample size: 177 Clinical setting: Primary care clinic Laboratory level: Intermediate Country: South Africa, Johannesburg World Bank Income Classification: Middle-income TB incidence rate: 993 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 1.4% (Source: Survey in Gauteng province, 2002) and among retreatment cases = 5.5% (Source: Survey in Gauteng province, 2002) Proportion of TB cases in the study: 37.9%		
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: Frozen Specimen Preparation: Processed Xpert MTB/RIF version: 1 and 2		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960		
Flow and timing			
Comparative			
Notes	One follow-up visit was performed approximately 60 days after enrolment Xpert MTB/RIF was performed on frozen specimens while MGIT culture and smear microscopy were performed on fresh specimens		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Teo 2011

Study characteristics			
Patient sampling	Prospective study with consecutive enrolment of participants		
Patient characteristics and setting	Presenting signs and symptoms: Patients thought to have TB based on symptoms and radiographic findings Age: Not stated Sex, female: Not stated HIV infection: Not stated History of TB: Not stated Sample size: 106 Clinical setting: University hospital Laboratory level: Central Country: Singapore World Bank Income Classification: High-income TB incidence rate: 37 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 0.6% (Source: Nationwide surveillance, 2011) and among retreatment cases = 0% (Source: Nationwide surveillance, 2011) Proportion of TB cases in the study: 58.5%		
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: Fresh Specimen Preparation: Processed Xpert MTB/RIF version: 1		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: Gene sequencing		
Flow and timing			
Comparative			
Notes	Respiratory specimens (predominantly sputum) submitted for routine testing; only one rifampicin-resistant isolate was identified		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	No		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	No		
		High	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Theron 2011

Study characteristics			
Patient sampling	Retrospective study with consecutive enrolment of participants		
Patient characteristics and setting	Presenting signs and symptoms: Patients presumed to have TB based on compatible signs and symptoms Age: Median 36 years; range 18 to 83 years Sex, female: 32.3% HIV infection: 31.3% History of TB: 34.3% Sample size: 480 Clinical setting: Two primary care clinics in a high HIV prevalence area Laboratory level: Intermediate Country: South Africa, Cape Town World Bank Income Classification: Middle-income TB incidence rate: 993 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 0.9% (Source: Survey in Western Cape Province, 2002) and among retreatment cases = 4.0% (Source: Survey in Western Cape Province, 2002) Proportion of TB cases in the study: 29.4%		
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: Frozen Specimen Preparation: Unprocessed Xpert MTB/RIF version: 1		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960		
Flow and timing			
Comparative			
Notes	Short-term follow-up cultures were obtained; 16 of 19 Xpert MTB/RIF-positive culture-negative patients were considered likely to be TB cases based on follow-up cultures, gene sequencing, and the presence of characteristic radiographic features using a standardised scoring system		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Theron 2011 (*Continued*)

		Low	

Van Rie 2013

Study characteristics			
Patient sampling	Cross-sectional design with consecutive enrolment of patients, prospective data collection		
Patient characteristics and setting	Presenting signs and symptoms: Prolonged (> two weeks) cough or other TB symptoms, or both, and had two prior-negative smear by fluorescence microscopy Age: Median 36 years (IQR 30 to 34) Sex, female: 56.8% HIV infection: 72.4% History of TB: 17.6% Sample size: 199 Clinical setting: Primary care clinic Laboratory level: Peripheral Country: South Africa, Johannesburg World Bank Income Classification: Middle-income TB incidence rate: 993 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 1.4% (Source: Survey in Gauteng province, 2002) and among retreatment cases = 5.5% (Source: Survey in Gauteng province, 2002) Proportion of TB cases in the study: 9.3%		
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Unprocessed Xpert MTB/RIF version: 3		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960		
Flow and timing			
Comparative			
Notes	Only those patients presumed to have TB who returned for results of the initial smear microscopy examinations were enrolled		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Were all patients included in the analysis?	No		
		High	

Williamson 2012

Study characteristics			
Patient sampling	Cross-sectional design with consecutive enrolment of smear-positive patients, prospective data collection		
Patient characteristics and setting	Presenting signs and symptoms: Clinical symptoms not reported: smear-positive specimens Age: > 15 years Sex, female: Not stated HIV infection: estimated < 1% History of TB: Not stated Sample size: 89 Clinical setting: Laboratory-based evaluation Laboratory level: Intermediate Country: New Zealand World Bank Income Classification: High-income TB incidence rate: 7.6 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 2.5% (Source: Nationwide surveillance 2009) and among retreatment cases = 13% (Source: Nationwide surveillance 2009) Proportion of TB cases in the study: 75.3%		
Index tests	Index: Xpert MTB/RIF assay Specimen condition: Fresh Specimen preparation: Processed Xpert MTB/RIF version: 3		
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: MGIT 960 Target condition: Rifampicin resistance Reference standard for rifampicin resistance: MGIT 960		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
		High	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	Yes		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Williamson 2012 (*Continued*)

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Zeka 2011

Study characteristics	
Patient sampling	Prospective study with consecutive enrolment of patients
Patient characteristics and setting	Presenting signs and symptoms: Clinical findings of possible TB Age: Median 48 years; range 25 to 70 years Sex, female: 42.4% HIV infection: Not stated History of TB: Not stated Sample size: 103 Clinical setting: Laboratory-based evaluation of routine sputum specimens at a university hospital Laboratory level: Intermediate Country: Turkey World Bank Income Classification: Middle-income TB incidence rate: 24 per 100,000 MDR-TB prevalence: Percent MDR-TB among new TB cases = 0.9% (Source: Survey in Ankara City 2011) and among retreatment cases = 38% (Source: Survey in Ankara City 2011) Proportion of TB cases in the study: 34.0%
Index tests	Index: Xpert MTB/RIF assay Specimen Condition: Frozen Specimen Preparation: Processed Xpert MTB/RIF version: 1
Target condition and reference standard(s)	Target condition: Pulmonary TB Reference standard for pulmonary TB: Löwenstein-Jensen culture and MB/MBacT liquid medium Target condition: Rifampicin resistance Reference standard for rifampicin resistance: Proportion method on 7H10 media
Flow and timing	
Comparative	
Notes	Only one rifampicin resistant isolate was identified. Data for sputum specimens were provided by the study author
Methodological quality	

Zeka 2011 (*Continued*)

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results for TB detection interpreted without knowledge of the results of the index test?	No		
Were the reference standard results for rifampicin resistance detection interpreted without knowledge of the results of the index test?	No		
		High	**Low**
DOMAIN 4: Flow and Timing			

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alvarez-Uria 2012	Reference standard not satisfied.
Andersen 2011	Editorial and comment.
Armand 2011	This was a case-control study that compared Xpert MTB/RIF with an in-house IS6110-based real-time PCR using TaqMan probes (IS6110-TaqMan assay) for TB detection
Banada 2010	Technical paper.
Bates 2013	This study evaluated Xpert MTB/RIF for the diagnosis of TB in children
Blakemore 2010	Technical paper.
Blakemore 2011	This was a technical paper that compared bacterial load quantitation determined by Xpert MTB/RIF with the load determined by conventional quantitative methods
Causse 2011	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB
Chegou 2011	Narrative review.
Clouse 2012	Study on patient impact.
Cuevas 2011	Narrative review.
Dorjee 2012	Case report.
Dorman 2012	Prevalence survey.
Dowdy 2011	Cost-effectiveness study.

(*Continued*)

Evans 2011	Editorial and comment.
Farga 2011	Narrative review.
Fenner 2011	Editorial and comment.
Ferrara 2011	Editorial and comment.
FIND 2011	This study compared Xpert MTB/RIF G3 and G4. We excluded it because of concern about duplicate data. In addtion, the crieria for the reference standard for rifampicin resistance detection were not satisfied
Friedrich 2011a	This study evaluated Xpert MTB/RIF for the diagnosis of pleural TB
Gotuzzo 2011	Editorial and comment.
Hesseling 2011	Editorial and comment.
Hillemann 2011	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB
Hoek 2011	Narrative review.
Ioannidis 2010	We could not obtain this article.
Kim 2012	Case-control study.
Kirwan 2012	Editorial and comment.
Lawn 2011a	This was a narrative review that covered the development, technical details, and diagnostic accuracy of Xpert MTB/RIF in adults and children
Lawn 2011b	Editorial and comment.
Lawn 2012	Study on patient impact.
Lawn 2012a	Data insufficient for 2 x 2 table.
Lawn 2012b	Correspondence.
Lawn 2012c	Primarily a lipoarabinomannan detection study.
Lawn 2012d	Duplicate data.
Ligthelm 2011	This study evaluated Xpert MTB/RIF for the diagnosis of TB lymphadenitis
Melzer 2011	Editorial and comment.
Miotto 2012	Treatment monitoring.
Morris 2010	Editorial and comment.

(*Continued*)

Morris 2011	Editorial and comment.
Moure 2012	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB
Muñoz 2013	Study on patient impact.
Narasimooloo 2012	Study on patient impact.
Nhu 2013	This study evaluated Xpert MTB/RIF for the diagnosis of TB in children
Nicol 2011	This study evaluated Xpert for the diagnosis of TB in children
Ntinginya 2012	This study included both adults and children. The study used an active case finding strategy involving previously known TB cases and identified five additional culture-confirmed TB cases (5/219). Xpert MTB/RIF showed a positive result in all five culture-confirmed TB cases (sensitivity = 100%). We considered the study design to be different from a diagnostic test accuracy study and therefore did not include this study in the review
O'Grady 2012	This study evaluated Xpert MTB/RIF in patients able to produce sputum, irrespective of admission diagnosis, not presumed TB patients
Perkins 2011	Correspondence.
Peter 2012a	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB
Peters 2012	Correspondence.
Rachow 2012	This study evaluated Xpert for the diagnosis of TB in children
Salvo 2011	Editorial and comment.
Scott 2012	Technical paper.
Swaminathan 2012	Relevance. This study disucssed lipoarabinomannan.
Tansey 2009	Editorial and comment.
Taylor 2012	This study evaluated Xpert for the diagnosis of extrapulmonary TB
Theron 2011a	Editorial and comment.
Theron 2012	Treatment monitoring.
Theron 2012a	Duplicate data.
Theron 2012b	Duplicate data.
Tortoli 2012	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB

(*Continued*)

Trebucq 2012	Editorial and comment.
Trebucq 2012a	Correspondence.
Vadwai 2011	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB
Vadwai 2012	Correspondence.
Van Rie 2010	This was a review that covered technical details of Xpert MTB/RIF and the test's potential value as a point-of-care test
Van Rie 2011	Case report.
van Zyl-Smit 2011	Technical paper.
Walters 2012	This study evaluated Xpert MTB/RIF for the diagnosis of TB in children
Williamson 2012a	Case-control study.
Wood 2012	This study evaluated Xpert MTB/RIF for the diagnosis of extrapulmonary TB
Yoon 2012	Duplicate data.
Zar 2012	This study evaluated Xpert MTB/RIF for the diagnosis of TB in children

Characteristics of ongoing studies *[ordered by study ID]*

Durovni 2013

Trial name or title	GeneXpert MTB/RIF, a new tool for the diagnosis of pulmonary tuberculosis in two municipalities in Brazil
Target condition and reference standard(s)	TB cases bacteriologically confirmed
Index and comparator tests	Xpert MTB/RIF assay and smear microscopy
Starting date	January 2012
Contact information	Betina Durovni bdurovni@saude.rio.rj.br
Notes	Group-randomized pragmatic trial following a stepped-wedge design. Identifier: NCT01363765

Luetkemeyer 2012

Trial name or title	Evaluation of Xpert MTB/RIF assay for the rapid identification of TB and TB rifampin resistance in HIV-infected and HIV-uninfected patients with presumed pulmonary tuberculosis
Target condition and reference standard(s)	TB: reference standard: MGIT culture
Index and comparator tests	Xpert MTB/RIF assay
Starting date	24 April 2012
Contact information	Jay (John) Dwyer jdwyer@php.ucsf.edu
Notes	Cohort study of diagnostic accuracy of Xpert MTB/RIF in HIV-infected and HIV-uninfected patients presumed to have pulmonary TB. Identifier: NCT01587469

Peter 2012

Trial name or title	A randomised control trial of sputum induction, and new and emerging technologies in a high HIV prevalence primary care setting
Target condition and reference standard(s)	TB: liquid culture
Index and comparator tests	Xpert MTB/RIF assay
Starting date	August 2009
Contact information	Jonny Peter Jonny.Peter@uct.ac.za
Notes	RCT to evaluate sputum induction for TB diagnosis in a primary care clinic for adults presumed to have TB. Identifier: NCT01545661

DATA

Presented below are all the data for all of the tests entered into the review.

Tests. Data tables by test

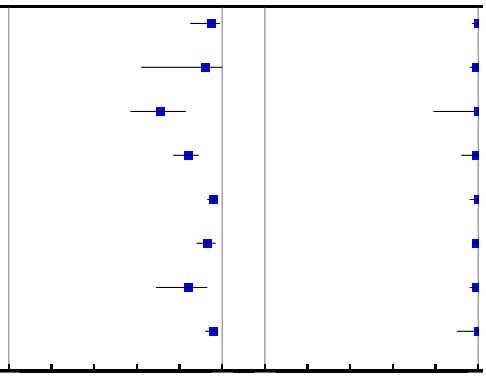
Test	No. of studies	No. of participants
1 TB detection, all studies	36	9557
2 Add on	33	7264
3 Smear positive	33	2020
4 Smear negative	33	7264
5 HIV positive	15	2474
6 HIV negative	18	2555
7 TB detection, condition of specimen	36	9557
8 TB detection, specimen preparation	36	9557
9 Proportion TB cases	36	9557
10 Income status	36	9557
11 RIF resistance detect	33	2966
12 Xpert version	33	2966
13 Proportion RIF resistance	33	2966

Test 1. TB detection, all studies.

Review: Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Test: 1 TB detection, all studies

Study	TP	FP	FN	TN	Sensitivity	Specificity
Al-Ateah 2012	42	0	2	128	0.95 [0.85, 0.99]	1.00 [0.97, 1.00]
Balcells 2012	11	1	1	147	0.92 [0.62, 1.00]	0.99 [0.96, 1.00]
Barnard 2012	37	0	15	16	0.71 [0.57, 0.83]	1.00 [0.79, 1.00]
Boehme 2010a	123	1	24	68	0.84 [0.77, 0.89]	0.99 [0.92, 1.00]
Boehme 2010b	201	0	8	101	0.96 [0.93, 0.98]	1.00 [0.96, 1.00]
Boehme 2010c	136	1	10	185	0.93 [0.88, 0.97]	0.99 [0.97, 1.00]
Boehme 2010d	36	3	7	215	0.84 [0.69, 0.93]	0.99 [0.96, 1.00]
Boehme 2010e	179	0	8	35	0.96 [0.92, 0.98]	1.00 [0.90, 1.00]



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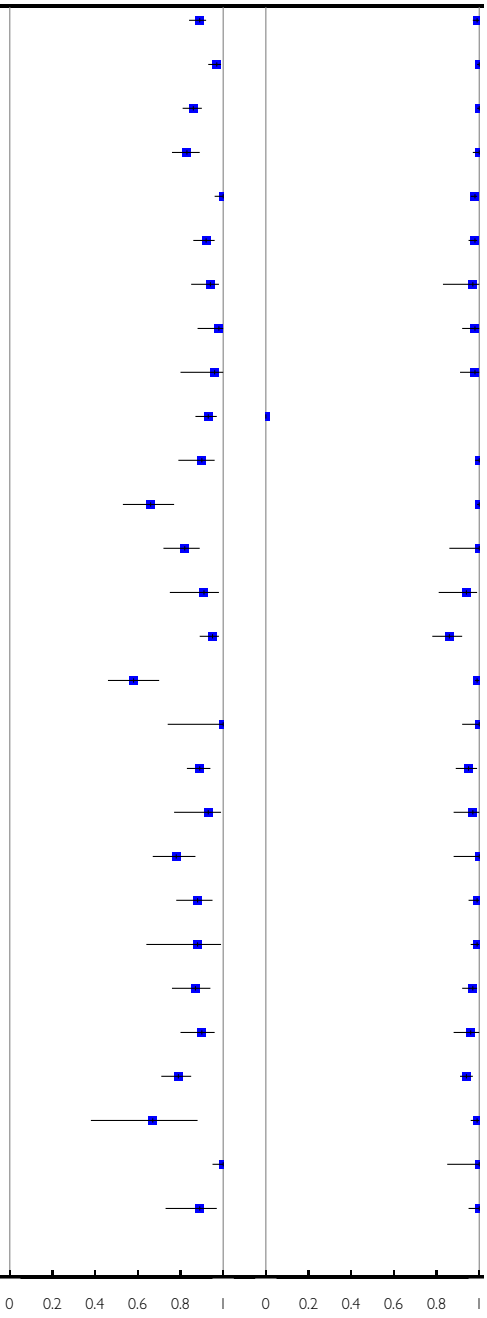
Study	TP	FP	FN	TN	Sensitivity	Specificity
Boehme 2011a	203	4	26	303	0.89 [0.84, 0.92]	0.99 [0.97, 1.00]
Boehme 2011b	171	3	6	825	0.97 [0.93, 0.99]	1.00 [0.99, 1.00]
Boehme 2011c	201	2	32	669	0.86 [0.81, 0.90]	1.00 [0.99, 1.00]
Boehme 2011d	121	0	24	144	0.83 [0.76, 0.89]	1.00 [0.97, 1.00]
Boehme 2011e	101	16	0	671	1.00 [0.96, 1.00]	0.98 [0.96, 0.99]
Boehme 2011f	136	5	12	234	0.92 [0.86, 0.96]	0.98 [0.95, 0.99]
Bowles 2011	60	1	4	29	0.94 [0.85, 0.98]	0.97 [0.83, 1.00]
Carriquiry 2012	44	2	1	84	0.98 [0.88, 1.00]	0.98 [0.92, 1.00]
Ciftci 2011	24	1	1	59	0.96 [0.80, 1.00]	0.98 [0.91, 1.00]
Friedrich 2011	117	0	9	0	0.93 [0.87, 0.97]	0.0 [0.0, 0.0]
Hanif 2011	54	0	6	146	0.90 [0.79, 0.96]	1.00 [0.98, 1.00]
Hanrahan 2013	42	2	22	487	0.66 [0.53, 0.77]	1.00 [0.99, 1.00]
Helb 2010	67	0	15	25	0.82 [0.72, 0.89]	1.00 [0.86, 1.00]
Ioannidis 2011	29	2	3	33	0.91 [0.75, 0.98]	0.94 [0.81, 0.99]
Kurbatova 2013	102	17	5	104	0.95 [0.89, 0.98]	0.86 [0.78, 0.92]
Lawn 2011	42	2	30	320	0.58 [0.46, 0.70]	0.99 [0.98, 1.00]
Malbruny 2011	12	0	0	46	1.00 [0.74, 1.00]	1.00 [0.92, 1.00]
Marlowe 2011	116	4	14	82	0.89 [0.83, 0.94]	0.95 [0.89, 0.99]
Miller 2011	27	2	2	58	0.93 [0.77, 0.99]	0.97 [0.88, 1.00]
Moure 2011	61	0	17	29	0.78 [0.67, 0.87]	1.00 [0.88, 1.00]
Rachow 2011	61	1	8	102	0.88 [0.78, 0.95]	0.99 [0.95, 1.00]
Safianowska 2012	15	1	2	127	0.88 [0.64, 0.99]	0.99 [0.96, 1.00]
Scott 2011	58	3	9	107	0.87 [0.76, 0.94]	0.97 [0.92, 0.99]
Teo 2011	56	2	6	55	0.90 [0.80, 0.96]	0.96 [0.88, 1.00]
Theron 2011	111	19	30	320	0.79 [0.71, 0.85]	0.94 [0.91, 0.97]
Van Rie 2013	10	1	5	145	0.67 [0.38, 0.88]	0.99 [0.96, 1.00]
Williamson 2012	67	0	0	22	1.00 [0.95, 1.00]	1.00 [0.85, 1.00]
Zeka 2011	31	0	4	68	0.89 [0.73, 0.97]	1.00 [0.95, 1.00]

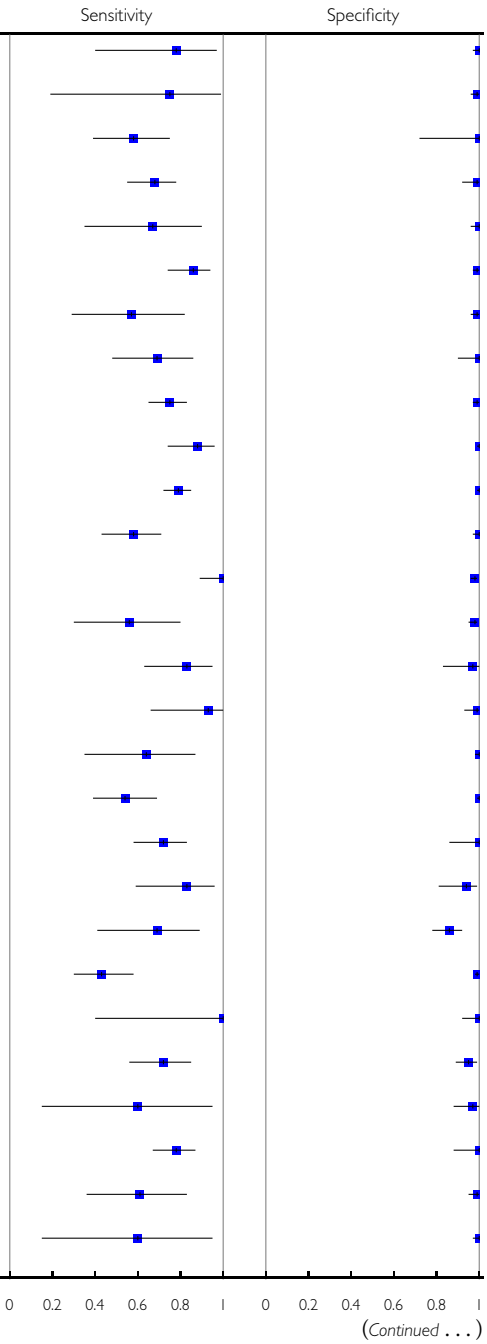


Test 2. Add on.

Review: Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Test: 2 Add on

Study	TP	FP	FN	TN	Sensitivity	Specificity
Al-Ateah 2012	7	0	2	127	0.78 [0.40, 0.97]	1.00 [0.97, 1.00]
Balcells 2012	3	1	1	145	0.75 [0.19, 0.99]	0.99 [0.96, 1.00]
Barnard 2012	18	0	13	11	0.58 [0.39, 0.75]	1.00 [0.72, 1.00]
Boehme 2010a	46	1	22	68	0.68 [0.55, 0.78]	0.99 [0.92, 1.00]
Boehme 2010b	8	0	4	101	0.67 [0.35, 0.90]	1.00 [0.96, 1.00]
Boehme 2010c	44	1	7	185	0.86 [0.74, 0.94]	0.99 [0.97, 1.00]
Boehme 2010d	8	3	6	215	0.57 [0.29, 0.82]	0.99 [0.96, 1.00]
Boehme 2010e	18	0	8	35	0.69 [0.48, 0.86]	1.00 [0.90, 1.00]
Boehme 2011a	68	4	23	303	0.75 [0.65, 0.83]	0.99 [0.97, 1.00]
Boehme 2011b	37	3	5	825	0.88 [0.74, 0.96]	1.00 [0.99, 1.00]
Boehme 2011c	121	2	32	669	0.79 [0.72, 0.85]	1.00 [0.99, 1.00]
Boehme 2011d	30	0	22	144	0.58 [0.43, 0.71]	1.00 [0.97, 1.00]
Boehme 2011e	31	16	0	671	1.00 [0.89, 1.00]	0.98 [0.96, 0.99]
Boehme 2011f	9	5	7	234	0.56 [0.30, 0.80]	0.98 [0.95, 0.99]
Bowles 2011	20	1	4	29	0.83 [0.63, 0.95]	0.97 [0.83, 1.00]
Carriquiry 2012	13	1	1	82	0.93 [0.66, 1.00]	0.99 [0.93, 1.00]
Hanif 2011	9	0	5	146	0.64 [0.35, 0.87]	1.00 [0.98, 1.00]
Hanrahan 2013	26	2	22	478	0.54 [0.39, 0.69]	1.00 [0.99, 1.00]
Helb 2010	38	0	15	25	0.72 [0.58, 0.83]	1.00 [0.86, 1.00]
Ioannidis 2011	15	2	3	33	0.83 [0.59, 0.96]	0.94 [0.81, 0.99]
Kurbatova 2013	11	17	5	104	0.69 [0.41, 0.89]	0.86 [0.78, 0.92]
Lawn 2011	23	2	30	320	0.43 [0.30, 0.58]	0.99 [0.98, 1.00]
Malbruny 2011	4	0	0	45	1.00 [0.40, 1.00]	1.00 [0.92, 1.00]
Marlowe 2011	31	4	12	82	0.72 [0.56, 0.85]	0.95 [0.89, 0.99]
Miller 2011	3	2	2	58	0.60 [0.15, 0.95]	0.97 [0.88, 1.00]
Moure 2011	61	0	17	29	0.78 [0.67, 0.87]	1.00 [0.88, 1.00]
Rachow 2011	11	1	7	102	0.61 [0.36, 0.83]	0.99 [0.95, 1.00]
Safianowska 2012	3	0	2	120	0.60 [0.15, 0.95]	1.00 [0.97, 1.00]



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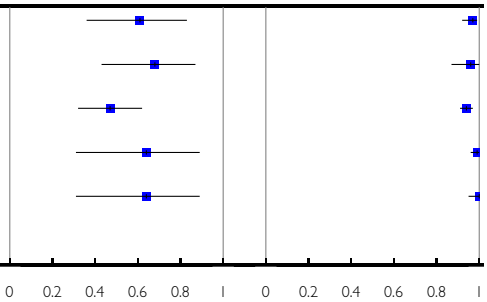
Study	TP	FP	FN	TN	Sensitivity	Specificity
Scott 2011	11	3	7	107	0.61 [0.36, 0.83]	0.97 [0.92, 0.99]
Teo 2011	13	2	6	49	0.68 [0.43, 0.87]	0.96 [0.87, 1.00]
Theron 2011	22	19	25	320	0.47 [0.32, 0.62]	0.94 [0.91, 0.97]
Van Rie 2013	7	1	4	142	0.64 [0.31, 0.89]	0.99 [0.96, 1.00]
Zeka 2011	7	0	4	68	0.64 [0.31, 0.89]	1.00 [0.95, 1.00]

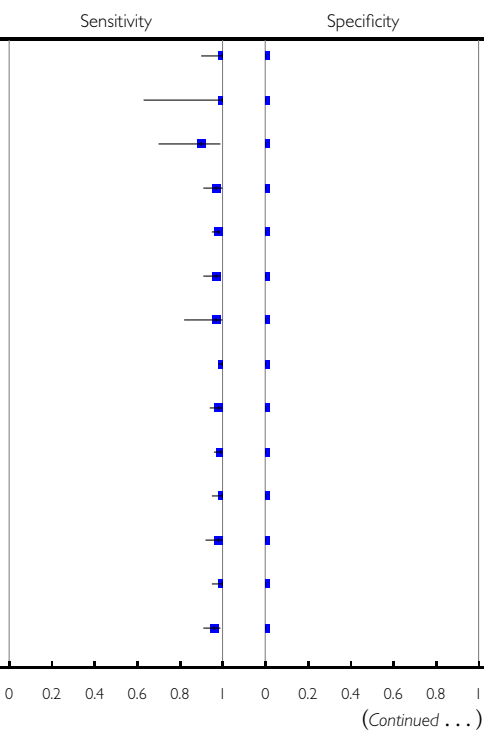


Test 3. Smear positive.

Review: Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Test: 3 Smear positive

Study	TP	FP	FN	TN	Sensitivity	Specificity
Al-Ateah 2012	35	0	0	0	1.00 [0.90, 1.00]	0.0 [0.0, 0.0]
Balcells 2012	8	0	0	0	1.00 [0.63, 1.00]	0.0 [0.0, 0.0]
Barnard 2012	19	0	2	0	0.90 [0.70, 0.99]	0.0 [0.0, 0.0]
Boehme 2010a	77	0	2	0	0.97 [0.91, 1.00]	0.0 [0.0, 0.0]
Boehme 2010b	193	0	4	0	0.98 [0.95, 0.99]	0.0 [0.0, 0.0]
Boehme 2010c	92	0	3	0	0.97 [0.91, 0.99]	0.0 [0.0, 0.0]
Boehme 2010d	28	0	1	0	0.97 [0.82, 1.00]	0.0 [0.0, 0.0]
Boehme 2010e	161	0	0	0	1.00 [0.98, 1.00]	0.0 [0.0, 0.0]
Boehme 2011a	135	0	3	0	0.98 [0.94, 1.00]	0.0 [0.0, 0.0]
Boehme 2011b	134	0	1	0	0.99 [0.96, 1.00]	0.0 [0.0, 0.0]
Boehme 2011c	80	0	0	0	1.00 [0.95, 1.00]	0.0 [0.0, 0.0]
Boehme 2011d	91	0	2	0	0.98 [0.92, 1.00]	0.0 [0.0, 0.0]
Boehme 2011e	70	0	0	0	1.00 [0.95, 1.00]	0.0 [0.0, 0.0]
Boehme 2011f	127	0	5	0	0.96 [0.91, 0.99]	0.0 [0.0, 0.0]



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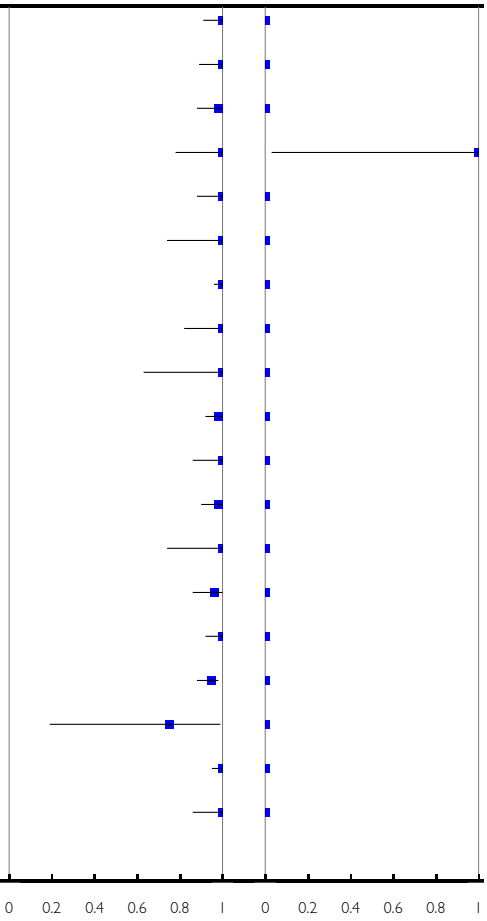
Study	TP	FP	FN	TN	Sensitivity	Specificity
Bowles 2011	40	0	0	0	1.00 [0.91, 1.00]	0.0 [0.0, 0.0]
Carriquiry 2012	31	0	0	0	1.00 [0.89, 1.00]	0.0 [0.0, 0.0]
Hanif 2011	45	0	1	0	0.98 [0.88, 1.00]	0.0 [0.0, 0.0]
Hanrahan 2013	15	0	0	1	1.00 [0.78, 1.00]	1.00 [0.03, 1.00]
Helb 2010	29	0	0	0	1.00 [0.88, 1.00]	0.0 [0.0, 0.0]
Ioannidis 2011	12	0	0	0	1.00 [0.74, 1.00]	0.0 [0.0, 0.0]
Kurbatova 2013	91	0	0	0	1.00 [0.96, 1.00]	0.0 [0.0, 0.0]
Lawn 2011	19	0	0	0	1.00 [0.82, 1.00]	0.0 [0.0, 0.0]
Malbruny 2011	8	0	0	0	1.00 [0.63, 1.00]	0.0 [0.0, 0.0]
Marlowe 2011	85	0	2	0	0.98 [0.92, 1.00]	0.0 [0.0, 0.0]
Miller 2011	24	0	0	0	1.00 [0.86, 1.00]	0.0 [0.0, 0.0]
Rachow 2011	50	0	1	0	0.98 [0.90, 1.00]	0.0 [0.0, 0.0]
Safianowska 2012	12	0	0	0	1.00 [0.74, 1.00]	0.0 [0.0, 0.0]
Scott 2011	47	0	2	0	0.96 [0.86, 1.00]	0.0 [0.0, 0.0]
Teo 2011	43	0	0	0	1.00 [0.92, 1.00]	0.0 [0.0, 0.0]
Theron 2011	89	0	5	0	0.95 [0.88, 0.98]	0.0 [0.0, 0.0]
Van Rie 2013	3	0	1	0	0.75 [0.19, 0.99]	0.0 [0.0, 0.0]
Williamson 2012	67	0	0	0	1.00 [0.95, 1.00]	0.0 [0.0, 0.0]
Zeka 2011	24	0	0	0	1.00 [0.86, 1.00]	0.0 [0.0, 0.0]

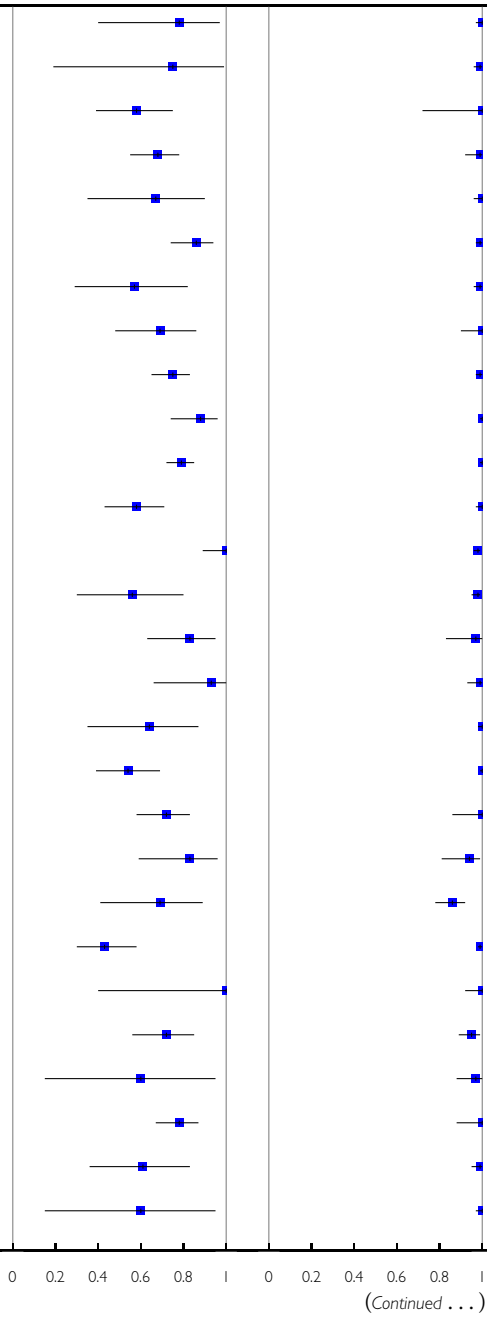


Test 4. Smear negative.

Review: Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Test: 4 Smear negative

Study	TP	FP	FN	TN	Sensitivity	Specificity
Al-Ateah 2012	7	0	2	127	0.78 [0.40, 0.97]	1.00 [0.97, 1.00]
Balcells 2012	3	1	1	145	0.75 [0.19, 0.99]	0.99 [0.96, 1.00]
Barnard 2012	18	0	13	11	0.58 [0.39, 0.75]	1.00 [0.72, 1.00]
Boehme 2010a	46	1	22	68	0.68 [0.55, 0.78]	0.99 [0.92, 1.00]
Boehme 2010b	8	0	4	101	0.67 [0.35, 0.90]	1.00 [0.96, 1.00]
Boehme 2010c	44	1	7	185	0.86 [0.74, 0.94]	0.99 [0.97, 1.00]
Boehme 2010d	8	3	6	215	0.57 [0.29, 0.82]	0.99 [0.96, 1.00]
Boehme 2010e	18	0	8	35	0.69 [0.48, 0.86]	1.00 [0.90, 1.00]
Boehme 2011a	68	4	23	303	0.75 [0.65, 0.83]	0.99 [0.97, 1.00]
Boehme 2011b	37	3	5	825	0.88 [0.74, 0.96]	1.00 [0.99, 1.00]
Boehme 2011c	121	2	32	669	0.79 [0.72, 0.85]	1.00 [0.99, 1.00]
Boehme 2011d	30	0	22	144	0.58 [0.43, 0.71]	1.00 [0.97, 1.00]
Boehme 2011e	31	16	0	671	1.00 [0.89, 1.00]	0.98 [0.96, 0.99]
Boehme 2011f	9	5	7	234	0.56 [0.30, 0.80]	0.98 [0.95, 0.99]
Bowles 2011	20	1	4	29	0.83 [0.63, 0.95]	0.97 [0.83, 1.00]
Carriquiry 2012	13	1	1	82	0.93 [0.66, 1.00]	0.99 [0.93, 1.00]
Hanif 2011	9	0	5	146	0.64 [0.35, 0.87]	1.00 [0.98, 1.00]
Hanrahan 2013	26	2	22	478	0.54 [0.39, 0.69]	1.00 [0.99, 1.00]
Helb 2010	38	0	15	25	0.72 [0.58, 0.83]	1.00 [0.86, 1.00]
Ioannidis 2011	15	2	3	33	0.83 [0.59, 0.96]	0.94 [0.81, 0.99]
Kurbatova 2013	11	17	5	104	0.69 [0.41, 0.89]	0.86 [0.78, 0.92]
Lawn 2011	23	2	30	320	0.43 [0.30, 0.58]	0.99 [0.98, 1.00]
Malbruny 2011	4	0	0	45	1.00 [0.40, 1.00]	1.00 [0.92, 1.00]
Marlowe 2011	31	4	12	82	0.72 [0.56, 0.85]	0.95 [0.89, 0.99]
Miller 2011	3	2	2	58	0.60 [0.15, 0.95]	0.97 [0.88, 1.00]
Moure 2011	61	0	17	29	0.78 [0.67, 0.87]	1.00 [0.88, 1.00]
Rachow 2011	11	1	7	102	0.61 [0.36, 0.83]	0.99 [0.95, 1.00]
Safianowska 2012	3	0	2	120	0.60 [0.15, 0.95]	1.00 [0.97, 1.00]



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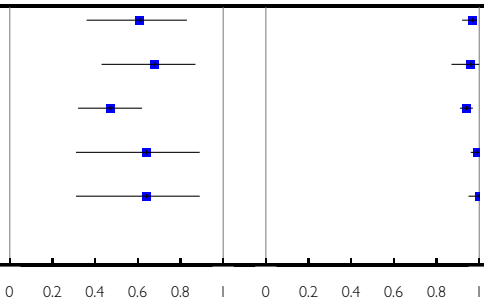
Study	TP	FP	FN	TN	Sensitivity	Specificity
Scott 2011	11	3	7	107	0.61 [0.36, 0.83]	0.97 [0.92, 0.99]
Teo 2011	13	2	6	49	0.68 [0.43, 0.87]	0.96 [0.87, 1.00]
Theron 2011	22	19	25	320	0.47 [0.32, 0.62]	0.94 [0.91, 0.97]
Van Rie 2013	7	1	4	142	0.64 [0.31, 0.89]	0.99 [0.96, 1.00]
Zeka 2011	7	0	4	68	0.64 [0.31, 0.89]	1.00 [0.95, 1.00]

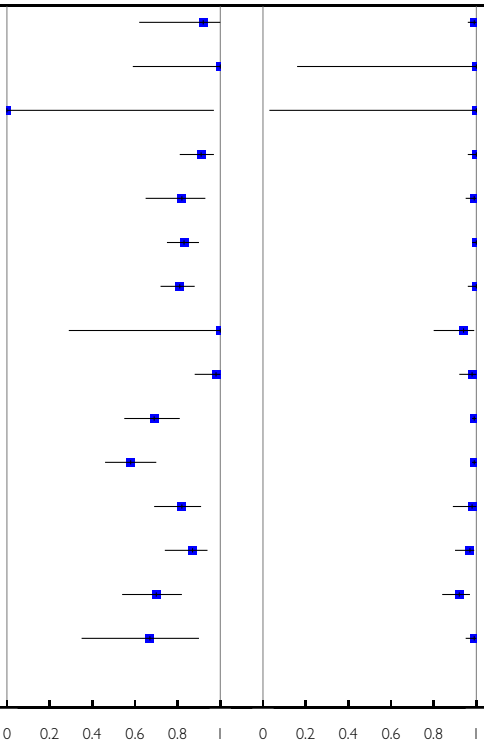


Test 5. HIV positive.

Review: Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Test: 5 HIV positive

Study	TP	FP	FN	TN	Sensitivity	Specificity
Balcells 2012	11	1	1	147	0.92 [0.62, 1.00]	0.99 [0.96, 1.00]
Boehme 2010a	7	0	0	2	1.00 [0.59, 1.00]	1.00 [0.16, 1.00]
Boehme 2010b	0	0	1	1	0.0 [0.0, 0.97]	1.00 [0.03, 1.00]
Boehme 2010c	60	0	6	81	0.91 [0.81, 0.97]	1.00 [0.96, 1.00]
Boehme 2010d	27	2	6	141	0.82 [0.65, 0.93]	0.99 [0.95, 1.00]
Boehme 2011c	90	1	18	263	0.83 [0.75, 0.90]	1.00 [0.98, 1.00]
Boehme 2011d	80	0	19	88	0.81 [0.72, 0.88]	1.00 [0.96, 1.00]
Boehme 2011e	3	2	0	31	1.00 [0.29, 1.00]	0.94 [0.80, 0.99]
Carriquiry 2012	44	2	1	84	0.98 [0.88, 1.00]	0.98 [0.92, 1.00]
Hanrahan 2013	36	2	16	325	0.69 [0.55, 0.81]	0.99 [0.98, 1.00]
Lawn 2011	42	2	30	320	0.58 [0.46, 0.70]	0.99 [0.98, 1.00]
Rachow 2011	41	1	9	49	0.82 [0.69, 0.91]	0.98 [0.89, 1.00]
Scott 2011	45	3	7	84	0.87 [0.74, 0.94]	0.97 [0.90, 0.99]
Theron 2011	32	7	14	77	0.70 [0.54, 0.82]	0.92 [0.84, 0.97]
Van Rie 2013	8	1	4	99	0.67 [0.35, 0.90]	0.99 [0.95, 1.00]

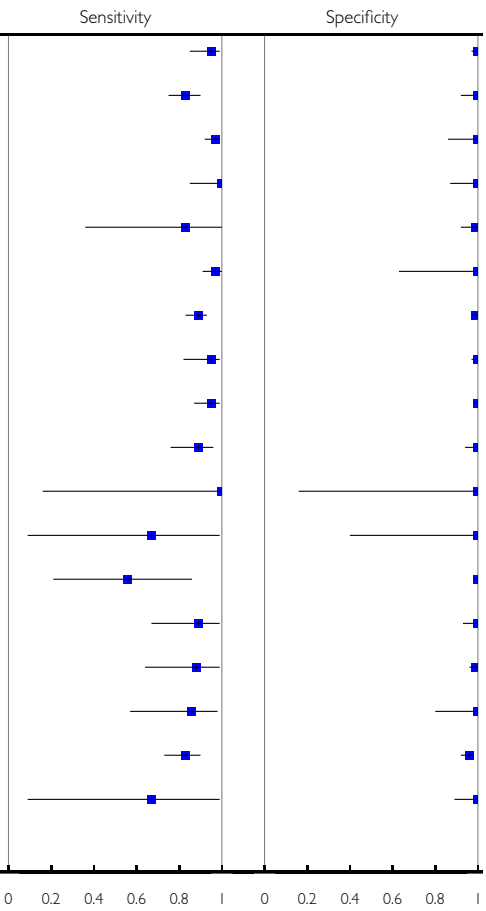


Test 6. HIV negative.

Review: Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Test: 6 HIV negative

Study	TP	FP	FN	TN	Sensitivity	Specificity
Al-Ateah 2012	42	0	2	127	0.95 [0.85, 0.99]	1.00 [0.97, 1.00]
Boehme 2010a	90	0	18	46	0.83 [0.75, 0.90]	1.00 [0.92, 1.00]
Boehme 2010b	142	0	5	24	0.97 [0.92, 0.99]	1.00 [0.86, 1.00]
Boehme 2010c	23	0	0	26	1.00 [0.85, 1.00]	1.00 [0.87, 1.00]
Boehme 2010d	5	1	1	69	0.83 [0.36, 1.00]	0.99 [0.92, 1.00]
Boehme 2010e	75	0	2	8	0.97 [0.91, 1.00]	1.00 [0.63, 1.00]
Boehme 2011a	161	3	20	252	0.89 [0.83, 0.93]	0.99 [0.97, 1.00]
Boehme 2011b	36	1	2	202	0.95 [0.82, 0.99]	1.00 [0.97, 1.00]
Boehme 2011c	62	1	3	232	0.95 [0.87, 0.99]	1.00 [0.98, 1.00]
Boehme 2011d	41	0	5	56	0.89 [0.76, 0.96]	1.00 [0.94, 1.00]
Boehme 2011e	2	0	0	2	1.00 [0.16, 1.00]	1.00 [0.16, 1.00]
Boehme 2011f	2	0	1	4	0.67 [0.09, 0.99]	1.00 [0.40, 1.00]
Hanrahan 2013	5	0	4	182	0.56 [0.21, 0.86]	1.00 [0.98, 1.00]
Rachow 2011	17	0	2	53	0.89 [0.67, 0.99]	1.00 [0.93, 1.00]
Safianowska 2012	15	1	2	127	0.88 [0.64, 0.99]	0.99 [0.96, 1.00]
Scott 2011	12	0	2	17	0.86 [0.57, 0.98]	1.00 [0.80, 1.00]
Theron 2011	68	9	14	195	0.83 [0.73, 0.90]	0.96 [0.92, 0.98]
Van Rie 2013	2	0	1	33	0.67 [0.09, 0.99]	1.00 [0.89, 1.00]

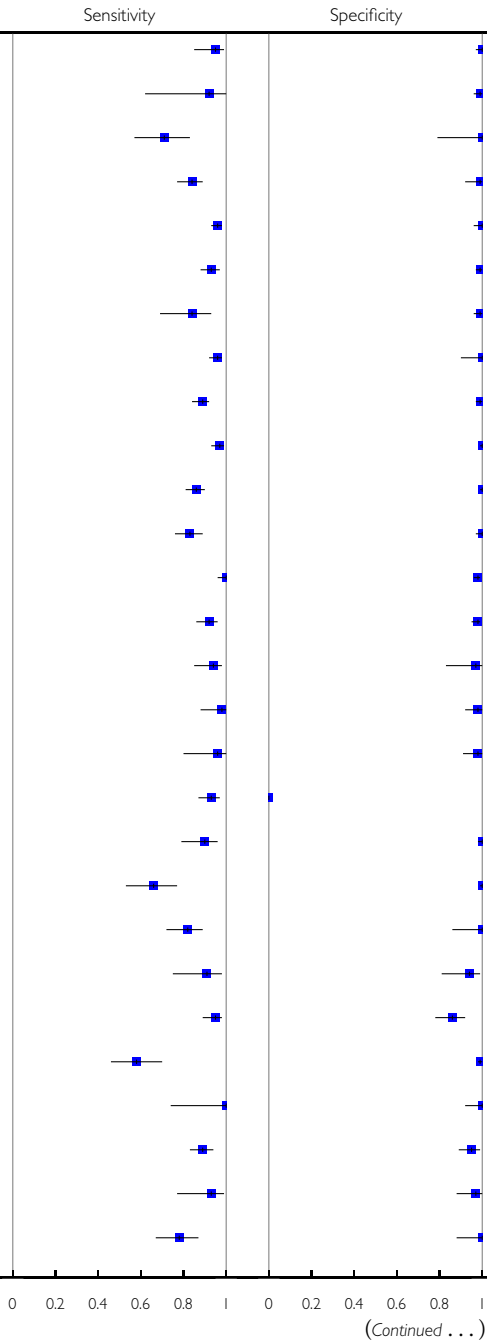


Test 7. TB detection, condition of specimen.

Review: Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Test: 7 TB detection, condition of specimen

Study	TP	FP	FN	TN	Sensitivity	Specificity
Al-Ateah 2012	42	0	2	128	0.95 [0.85, 0.99]	1.00 [0.97, 1.00]
Balcells 2012	11	1	1	147	0.92 [0.62, 1.00]	0.99 [0.96, 1.00]
Barnard 2012	37	0	15	16	0.71 [0.57, 0.83]	1.00 [0.79, 1.00]
Boehme 2010a	123	1	24	68	0.84 [0.77, 0.89]	0.99 [0.92, 1.00]
Boehme 2010b	201	0	8	101	0.96 [0.93, 0.98]	1.00 [0.96, 1.00]
Boehme 2010c	136	1	10	185	0.93 [0.88, 0.97]	0.99 [0.97, 1.00]
Boehme 2010d	36	3	7	215	0.84 [0.69, 0.93]	0.99 [0.96, 1.00]
Boehme 2010e	179	0	8	35	0.96 [0.92, 0.98]	1.00 [0.90, 1.00]
Boehme 2011a	203	4	26	303	0.89 [0.84, 0.92]	0.99 [0.97, 1.00]
Boehme 2011b	171	3	6	825	0.97 [0.93, 0.99]	1.00 [0.99, 1.00]
Boehme 2011c	201	2	32	669	0.86 [0.81, 0.90]	1.00 [0.99, 1.00]
Boehme 2011d	121	0	24	144	0.83 [0.76, 0.89]	1.00 [0.97, 1.00]
Boehme 2011e	101	16	0	671	1.00 [0.96, 1.00]	0.98 [0.96, 0.99]
Boehme 2011f	136	5	12	234	0.92 [0.86, 0.96]	0.98 [0.95, 0.99]
Bowles 2011	60	1	4	29	0.94 [0.85, 0.98]	0.97 [0.83, 1.00]
Carriquiry 2012	44	2	1	84	0.98 [0.88, 1.00]	0.98 [0.92, 1.00]
Ciftci 2011	24	1	1	59	0.96 [0.80, 1.00]	0.98 [0.91, 1.00]
Friedrich 2011	117	0	9	0	0.93 [0.87, 0.97]	0.0 [0.0, 0.0]
Hanif 2011	54	0	6	146	0.90 [0.79, 0.96]	1.00 [0.98, 1.00]
Hanrahan 2013	42	2	22	487	0.66 [0.53, 0.77]	1.00 [0.99, 1.00]
Helb 2010	67	0	15	25	0.82 [0.72, 0.89]	1.00 [0.86, 1.00]
Ioannidis 2011	29	2	3	33	0.91 [0.75, 0.98]	0.94 [0.81, 0.99]
Kurbatova 2013	102	17	5	104	0.95 [0.89, 0.98]	0.86 [0.78, 0.92]
Lawn 2011	42	2	30	320	0.58 [0.46, 0.70]	0.99 [0.98, 1.00]
Malbruny 2011	12	0	0	46	1.00 [0.74, 1.00]	1.00 [0.92, 1.00]
Marlowe 2011	116	4	14	82	0.89 [0.83, 0.94]	0.95 [0.89, 0.99]
Miller 2011	27	2	2	58	0.93 [0.77, 0.99]	0.97 [0.88, 1.00]
Moure 2011	61	0	17	29	0.78 [0.67, 0.87]	1.00 [0.88, 1.00]



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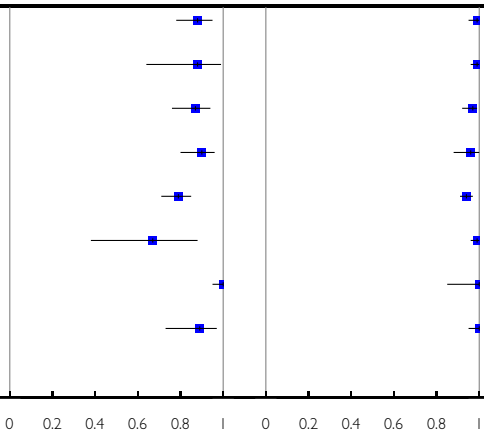
Study	TP	FP	FN	TN	Sensitivity	Specificity
Rachow 2011	61	1	8	102	0.88 [0.78, 0.95]	0.99 [0.95, 1.00]
Safianowska 2012	15	1	2	127	0.88 [0.64, 0.99]	0.99 [0.96, 1.00]
Scott 2011	58	3	9	107	0.87 [0.76, 0.94]	0.97 [0.92, 0.99]
Teo 2011	56	2	6	55	0.90 [0.80, 0.96]	0.96 [0.88, 1.00]
Theron 2011	111	19	30	320	0.79 [0.71, 0.85]	0.94 [0.91, 0.97]
Van Rie 2013	10	1	5	145	0.67 [0.38, 0.88]	0.99 [0.96, 1.00]
Williamson 2012	67	0	0	22	1.00 [0.95, 1.00]	1.00 [0.85, 1.00]
Zeka 2011	31	0	4	68	0.89 [0.73, 0.97]	1.00 [0.95, 1.00]

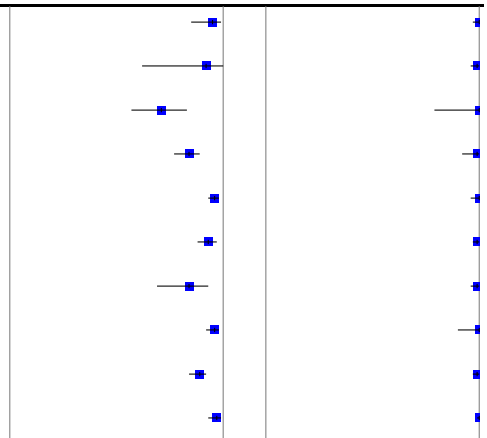


Test 8. TB detection, specimen preparation.

Review: Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Test: 8 TB detection, specimen preparation

Study	TP	FP	FN	TN	Sensitivity	Specificity
Al-Ateah 2012	42	0	2	128	0.95 [0.85, 0.99]	1.00 [0.97, 1.00]
Balcells 2012	11	1	1	147	0.92 [0.62, 1.00]	0.99 [0.96, 1.00]
Barnard 2012	37	0	15	16	0.71 [0.57, 0.83]	1.00 [0.79, 1.00]
Boehme 2010a	123	1	24	68	0.84 [0.77, 0.89]	0.99 [0.92, 1.00]
Boehme 2010b	201	0	8	101	0.96 [0.93, 0.98]	1.00 [0.96, 1.00]
Boehme 2010c	136	1	10	185	0.93 [0.88, 0.97]	0.99 [0.97, 1.00]
Boehme 2010d	36	3	7	215	0.84 [0.69, 0.93]	0.99 [0.96, 1.00]
Boehme 2010e	179	0	8	35	0.96 [0.92, 0.98]	1.00 [0.90, 1.00]
Boehme 2011a	203	4	26	303	0.89 [0.84, 0.92]	0.99 [0.97, 1.00]
Boehme 2011b	171	3	6	825	0.97 [0.93, 0.99]	1.00 [0.99, 1.00]
Boehme 2011c	201	2	32	669	0.86 [0.81, 0.90]	1.00 [0.99, 1.00]



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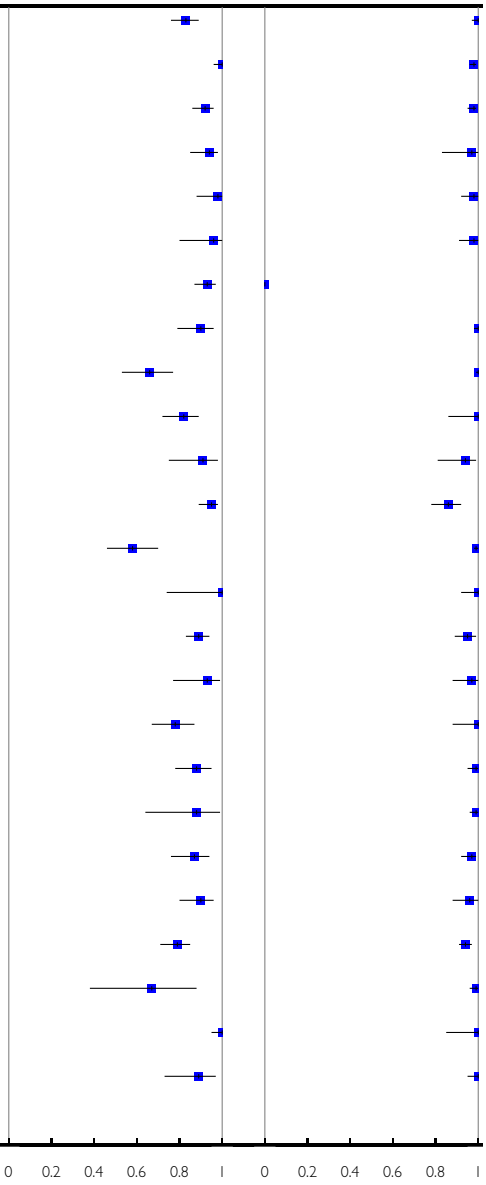
Study	TP	FP	FN	TN	Sensitivity	Specificity
Boehme 2011d	121	0	24	144	0.83 [0.76, 0.89]	1.00 [0.97, 1.00]
Boehme 2011e	101	16	0	671	1.00 [0.96, 1.00]	0.98 [0.96, 0.99]
Boehme 2011f	136	5	12	234	0.92 [0.86, 0.96]	0.98 [0.95, 0.99]
Bowles 2011	60	1	4	29	0.94 [0.85, 0.98]	0.97 [0.83, 1.00]
Carriquiry 2012	44	2	1	84	0.98 [0.88, 1.00]	0.98 [0.92, 1.00]
Ciftci 2011	24	1	1	59	0.96 [0.80, 1.00]	0.98 [0.91, 1.00]
Friedrich 2011	117	0	9	0	0.93 [0.87, 0.97]	0.0 [0.0, 0.0]
Hanif 2011	54	0	6	146	0.90 [0.79, 0.96]	1.00 [0.98, 1.00]
Hanrahan 2013	42	2	22	487	0.66 [0.53, 0.77]	1.00 [0.99, 1.00]
Helb 2010	67	0	15	25	0.82 [0.72, 0.89]	1.00 [0.86, 1.00]
Ioannidis 2011	29	2	3	33	0.91 [0.75, 0.98]	0.94 [0.81, 0.99]
Kurbatova 2013	102	17	5	104	0.95 [0.89, 0.98]	0.86 [0.78, 0.92]
Lawn 2011	42	2	30	320	0.58 [0.46, 0.70]	0.99 [0.98, 1.00]
Malbruny 2011	12	0	0	46	1.00 [0.74, 1.00]	1.00 [0.92, 1.00]
Marlowe 2011	116	4	14	82	0.89 [0.83, 0.94]	0.95 [0.89, 0.99]
Miller 2011	27	2	2	58	0.93 [0.77, 0.99]	0.97 [0.88, 1.00]
Moure 2011	61	0	17	29	0.78 [0.67, 0.87]	1.00 [0.88, 1.00]
Rachow 2011	61	1	8	102	0.88 [0.78, 0.95]	0.99 [0.95, 1.00]
Safianowska 2012	15	1	2	127	0.88 [0.64, 0.99]	0.99 [0.96, 1.00]
Scott 2011	58	3	9	107	0.87 [0.76, 0.94]	0.97 [0.92, 0.99]
Teo 2011	56	2	6	55	0.90 [0.80, 0.96]	0.96 [0.88, 1.00]
Theron 2011	111	19	30	320	0.79 [0.71, 0.85]	0.94 [0.91, 0.97]
Van Rie 2013	10	1	5	145	0.67 [0.38, 0.88]	0.99 [0.96, 1.00]
Williamson 2012	67	0	0	22	1.00 [0.95, 1.00]	1.00 [0.85, 1.00]
Zeka 2011	31	0	4	68	0.89 [0.73, 0.97]	1.00 [0.95, 1.00]

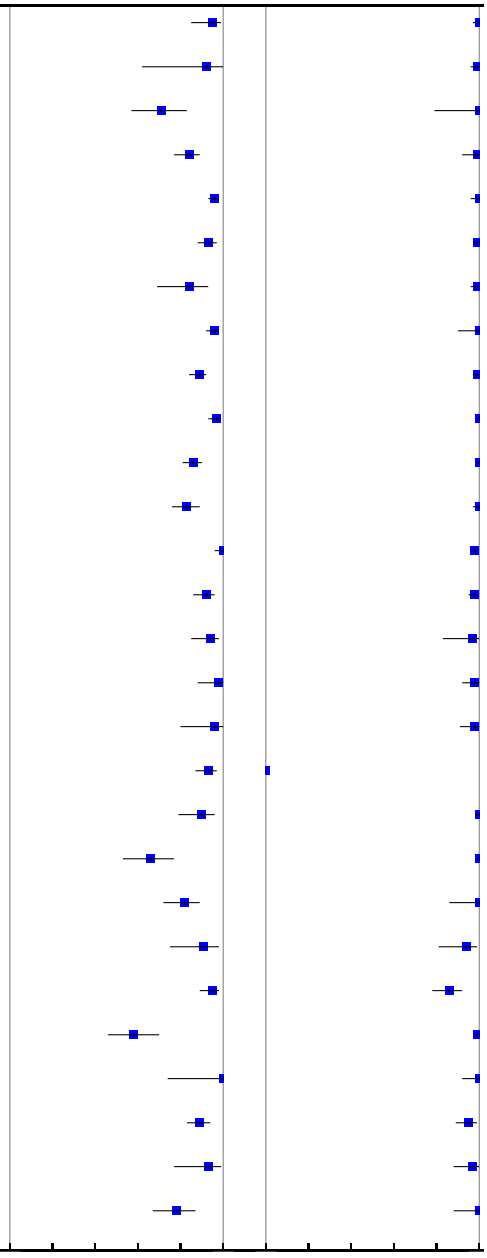


Test 9. Proportion TB cases.

Review: Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Test: 9 Proportion TB cases

Study	TP	FP	FN	TN	Sensitivity	Specificity
Al-Ateah 2012	42	0	2	128	0.95 [0.85, 0.99]	1.00 [0.97, 1.00]
Balcells 2012	11	1	1	147	0.92 [0.62, 1.00]	0.99 [0.96, 1.00]
Barnard 2012	37	0	15	16	0.71 [0.57, 0.83]	1.00 [0.79, 1.00]
Boehme 2010a	123	1	24	68	0.84 [0.77, 0.89]	0.99 [0.92, 1.00]
Boehme 2010b	201	0	8	101	0.96 [0.93, 0.98]	1.00 [0.96, 1.00]
Boehme 2010c	136	1	10	185	0.93 [0.88, 0.97]	0.99 [0.97, 1.00]
Boehme 2010d	36	3	7	215	0.84 [0.69, 0.93]	0.99 [0.96, 1.00]
Boehme 2010e	179	0	8	35	0.96 [0.92, 0.98]	1.00 [0.90, 1.00]
Boehme 2011a	203	4	26	303	0.89 [0.84, 0.92]	0.99 [0.97, 1.00]
Boehme 2011b	171	3	6	825	0.97 [0.93, 0.99]	1.00 [0.99, 1.00]
Boehme 2011c	201	2	32	669	0.86 [0.81, 0.90]	1.00 [0.99, 1.00]
Boehme 2011d	121	0	24	144	0.83 [0.76, 0.89]	1.00 [0.97, 1.00]
Boehme 2011e	101	16	0	671	1.00 [0.96, 1.00]	0.98 [0.96, 0.99]
Boehme 2011f	136	5	12	234	0.92 [0.86, 0.96]	0.98 [0.95, 0.99]
Bowles 2011	60	1	4	29	0.94 [0.85, 0.98]	0.97 [0.83, 1.00]
Carriquiry 2012	44	2	1	84	0.98 [0.88, 1.00]	0.98 [0.92, 1.00]
Ciftci 2011	24	1	1	59	0.96 [0.80, 1.00]	0.98 [0.91, 1.00]
Friedrich 2011	117	0	9	0	0.93 [0.87, 0.97]	0.0 [0.0, 0.0]
Hanif 2011	54	0	6	146	0.90 [0.79, 0.96]	1.00 [0.98, 1.00]
Hanrahan 2013	42	2	22	487	0.66 [0.53, 0.77]	1.00 [0.99, 1.00]
Helb 2010	67	0	15	25	0.82 [0.72, 0.89]	1.00 [0.86, 1.00]
Ioannidis 2011	29	2	3	33	0.91 [0.75, 0.98]	0.94 [0.81, 0.99]
Kurbatova 2013	102	17	5	104	0.95 [0.89, 0.98]	0.86 [0.78, 0.92]
Lawn 2011	42	2	30	320	0.58 [0.46, 0.70]	0.99 [0.98, 1.00]
Malbruny 2011	12	0	0	46	1.00 [0.74, 1.00]	1.00 [0.92, 1.00]
Marlowe 2011	116	4	14	82	0.89 [0.83, 0.94]	0.95 [0.89, 0.99]
Miller 2011	27	2	2	58	0.93 [0.77, 0.99]	0.97 [0.88, 1.00]
Moure 2011	61	0	17	29	0.78 [0.67, 0.87]	1.00 [0.88, 1.00]



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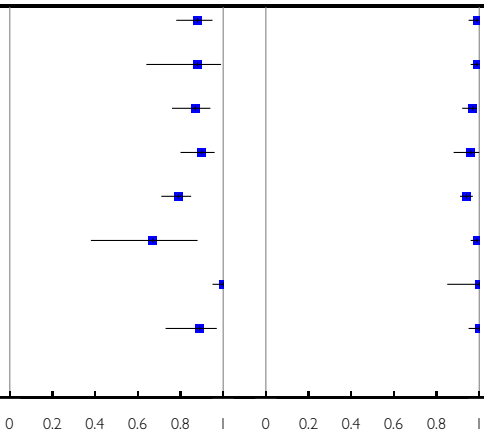
Study	TP	FP	FN	TN	Sensitivity	Specificity
Rachow 2011	61	1	8	102	0.88 [0.78, 0.95]	0.99 [0.95, 1.00]
Safianowska 2012	15	1	2	127	0.88 [0.64, 0.99]	0.99 [0.96, 1.00]
Scott 2011	58	3	9	107	0.87 [0.76, 0.94]	0.97 [0.92, 0.99]
Teo 2011	56	2	6	55	0.90 [0.80, 0.96]	0.96 [0.88, 1.00]
Theron 2011	111	19	30	320	0.79 [0.71, 0.85]	0.94 [0.91, 0.97]
Van Rie 2013	10	1	5	145	0.67 [0.38, 0.88]	0.99 [0.96, 1.00]
Williamson 2012	67	0	0	22	1.00 [0.95, 1.00]	1.00 [0.85, 1.00]
Zeka 2011	31	0	4	68	0.89 [0.73, 0.97]	1.00 [0.95, 1.00]

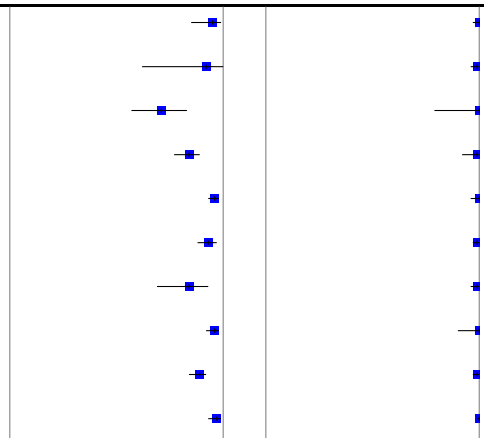


Test 10. Income status.

Review: Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Test: 10 Income status

Study	TP	FP	FN	TN	Sensitivity	Specificity
Al-Ateah 2012	42	0	2	128	0.95 [0.85, 0.99]	1.00 [0.97, 1.00]
Balcells 2012	11	1	1	147	0.92 [0.62, 1.00]	0.99 [0.96, 1.00]
Barnard 2012	37	0	15	16	0.71 [0.57, 0.83]	1.00 [0.79, 1.00]
Boehme 2010a	123	1	24	68	0.84 [0.77, 0.89]	0.99 [0.92, 1.00]
Boehme 2010b	201	0	8	101	0.96 [0.93, 0.98]	1.00 [0.96, 1.00]
Boehme 2010c	136	1	10	185	0.93 [0.88, 0.97]	0.99 [0.97, 1.00]
Boehme 2010d	36	3	7	215	0.84 [0.69, 0.93]	0.99 [0.96, 1.00]
Boehme 2010e	179	0	8	35	0.96 [0.92, 0.98]	1.00 [0.90, 1.00]
Boehme 2011a	203	4	26	303	0.89 [0.84, 0.92]	0.99 [0.97, 1.00]
Boehme 2011b	171	3	6	825	0.97 [0.93, 0.99]	1.00 [0.99, 1.00]
Boehme 2011c	201	2	32	669	0.86 [0.81, 0.90]	1.00 [0.99, 1.00]
Boehme 2011d	121	0	24	144	0.83 [0.76, 0.89]	1.00 [0.97, 1.00]



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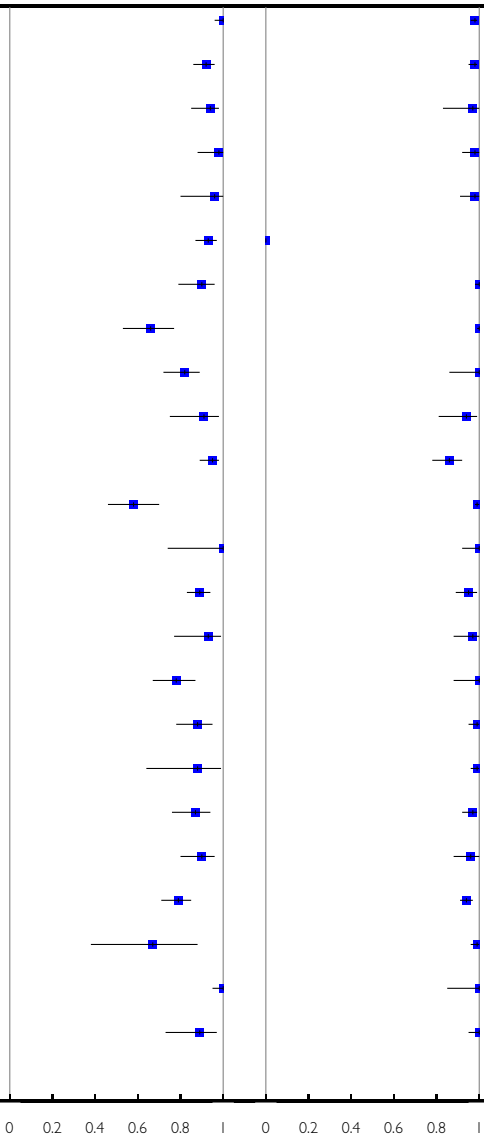
Study	TP	FP	FN	TN	Sensitivity	Specificity
Boehme 2011e	101	16	0	671	1.00 [0.96, 1.00]	0.98 [0.96, 0.99]
Boehme 2011f	136	5	12	234	0.92 [0.86, 0.96]	0.98 [0.95, 0.99]
Bowles 2011	60	1	4	29	0.94 [0.85, 0.98]	0.97 [0.83, 1.00]
Carriquiry 2012	44	2	1	84	0.98 [0.88, 1.00]	0.98 [0.92, 1.00]
Ciftci 2011	24	1	1	59	0.96 [0.80, 1.00]	0.98 [0.91, 1.00]
Friedrich 2011	117	0	9	0	0.93 [0.87, 0.97]	0.0 [0.0, 0.0]
Hanif 2011	54	0	6	146	0.90 [0.79, 0.96]	1.00 [0.98, 1.00]
Hanrahan 2013	42	2	22	487	0.66 [0.53, 0.77]	1.00 [0.99, 1.00]
Helb 2010	67	0	15	25	0.82 [0.72, 0.89]	1.00 [0.86, 1.00]
Ioannidis 2011	29	2	3	33	0.91 [0.75, 0.98]	0.94 [0.81, 0.99]
Kurbatova 2013	102	17	5	104	0.95 [0.89, 0.98]	0.86 [0.78, 0.92]
Lawn 2011	42	2	30	320	0.58 [0.46, 0.70]	0.99 [0.98, 1.00]
Malbruny 2011	12	0	0	46	1.00 [0.74, 1.00]	1.00 [0.92, 1.00]
Marlowe 2011	116	4	14	82	0.89 [0.83, 0.94]	0.95 [0.89, 0.99]
Miller 2011	27	2	2	58	0.93 [0.77, 0.99]	0.97 [0.88, 1.00]
Moure 2011	61	0	17	29	0.78 [0.67, 0.87]	1.00 [0.88, 1.00]
Rachow 2011	61	1	8	102	0.88 [0.78, 0.95]	0.99 [0.95, 1.00]
Safianowska 2012	15	1	2	127	0.88 [0.64, 0.99]	0.99 [0.96, 1.00]
Scott 2011	58	3	9	107	0.87 [0.76, 0.94]	0.97 [0.92, 0.99]
Teo 2011	56	2	6	55	0.90 [0.80, 0.96]	0.96 [0.88, 1.00]
Theron 2011	111	19	30	320	0.79 [0.71, 0.85]	0.94 [0.91, 0.97]
Van Rie 2013	10	1	5	145	0.67 [0.38, 0.88]	0.99 [0.96, 1.00]
Williamson 2012	67	0	0	22	1.00 [0.95, 1.00]	1.00 [0.85, 1.00]
Zeka 2011	31	0	4	68	0.89 [0.73, 0.97]	1.00 [0.95, 1.00]

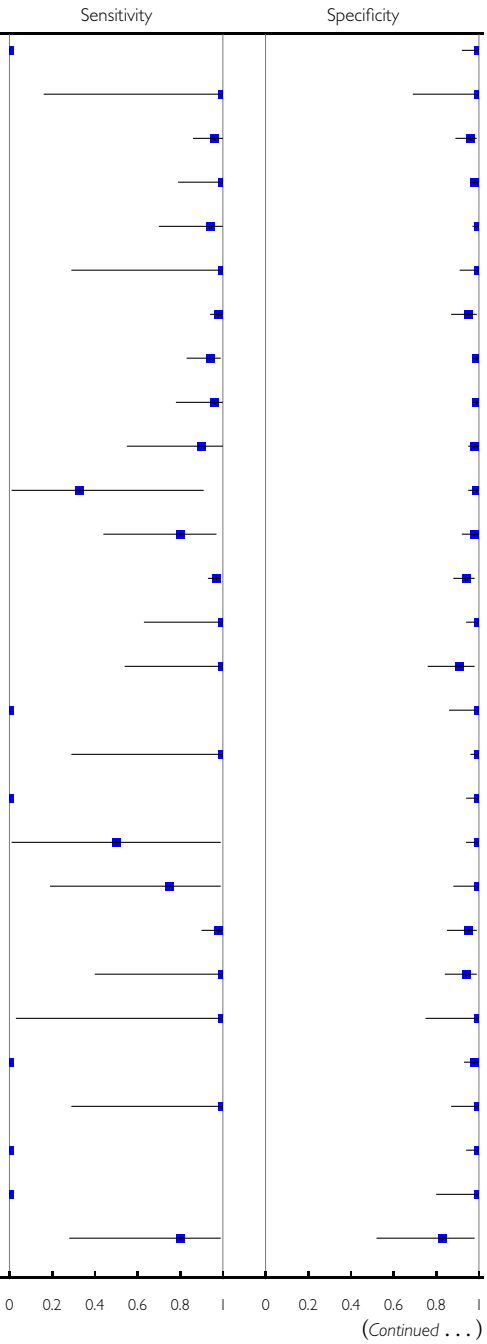


Test 11. RIF resistance detect.

Review: Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Test: 11 RIF resistance detect

Study	TP	FP	FN	TN	Sensitivity	Specificity
Al-Ateah 2012	0	0	0	44	0.0 [0.0, 0.0]	1.00 [0.92, 1.00]
Balcells 2012	2	0	0	10	1.00 [0.16, 1.00]	1.00 [0.69, 1.00]
Boehme 2010a	47	4	2	90	0.96 [0.86, 1.00]	0.96 [0.89, 0.99]
Boehme 2010b	16	3	0	190	1.00 [0.79, 1.00]	0.98 [0.96, 1.00]
Boehme 2010c	15	0	1	126	0.94 [0.70, 1.00]	1.00 [0.97, 1.00]
Boehme 2010d	3	0	0	38	1.00 [0.29, 1.00]	1.00 [0.91, 1.00]
Boehme 2010e	119	3	2	61	0.98 [0.94, 1.00]	0.95 [0.87, 0.99]
Boehme 2011a	47	1	3	160	0.94 [0.83, 0.99]	0.99 [0.97, 1.00]
Boehme 2011b	22	1	1	161	0.96 [0.78, 1.00]	0.99 [0.97, 1.00]
Boehme 2011c	9	3	1	175	0.90 [0.55, 1.00]	0.98 [0.95, 1.00]
Boehme 2011d	1	1	2	112	0.33 [0.01, 0.91]	0.99 [0.95, 1.00]
Boehme 2011e	8	2	2	91	0.80 [0.44, 0.97]	0.98 [0.92, 1.00]
Boehme 2011f	149	6	5	97	0.97 [0.93, 0.99]	0.94 [0.88, 0.98]
Bowles 2011	8	0	0	56	1.00 [0.63, 1.00]	1.00 [0.94, 1.00]
Carriquiry 2012	6	3	0	30	1.00 [0.54, 1.00]	0.91 [0.76, 0.98]
Ciftci 2011	0	0	0	25	0.0 [0.0, 0.0]	1.00 [0.86, 1.00]
Friedrich 2011	3	0	0	90	1.00 [0.29, 1.00]	1.00 [0.96, 1.00]
Hanif 2011	0	0	0	60	0.0 [0.0, 0.0]	1.00 [0.94, 1.00]
Hanrahan 2013	1	0	1	62	0.50 [0.01, 0.99]	1.00 [0.94, 1.00]
Ioannidis 2011	3	0	1	28	0.75 [0.19, 0.99]	1.00 [0.88, 1.00]
Kurbatova 2013	55	2	1	42	0.98 [0.90, 1.00]	0.95 [0.85, 0.99]
Lawn 2011	4	3	0	48	1.00 [0.40, 1.00]	0.94 [0.84, 0.99]
Malbruny 2011	1	0	0	13	1.00 [0.03, 1.00]	1.00 [0.75, 1.00]
Marlowe 2011	0	3	0	127	0.0 [0.0, 0.0]	0.98 [0.93, 1.00]
Miller 2011	3	0	0	26	1.00 [0.29, 1.00]	1.00 [0.87, 1.00]
Rachow 2011	0	0	0	59	0.0 [0.0, 0.0]	1.00 [0.94, 1.00]
Safianowska 2012	0	0	0	17	0.0 [0.0, 0.0]	1.00 [0.80, 1.00]
Scott 2011	4	2	1	10	0.80 [0.28, 0.99]	0.83 [0.52, 0.98]



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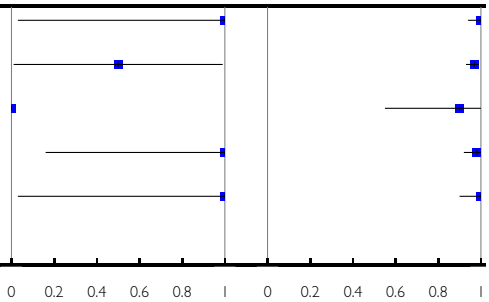
Study	TP	FP	FN	TN	Sensitivity	Specificity
Teo 2011	1	0	0	61	1.00 [0.03, 1.00]	1.00 [0.94, 1.00]
Theron 2011	1	5	1	151	0.50 [0.01, 0.99]	0.97 [0.93, 0.99]
Van Rie 2013	0	1	0	9	0.0 [0.0, 0.0]	0.90 [0.55, 1.00]
Williamson 2012	2	1	0	64	1.00 [0.16, 1.00]	0.98 [0.92, 1.00]
Zeka 2011	1	0	0	34	1.00 [0.03, 1.00]	1.00 [0.90, 1.00]

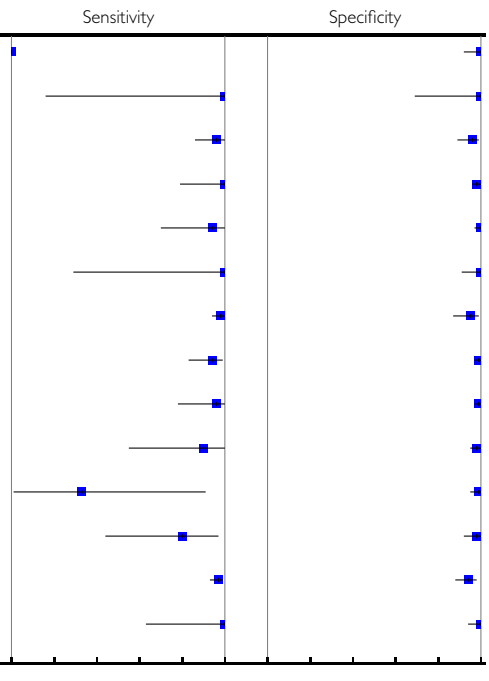


Test 12. Xpert version.

Review: Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Test: 12 Xpert version

Study	TP	FP	FN	TN	Sensitivity	Specificity
Al-Ateah 2012	0	0	0	44	0.0 [0.0, 0.0]	1.00 [0.92, 1.00]
Balcells 2012	2	0	0	10	1.00 [0.16, 1.00]	1.00 [0.69, 1.00]
Boehme 2010a	47	4	2	90	0.96 [0.86, 1.00]	0.96 [0.89, 0.99]
Boehme 2010b	16	3	0	190	1.00 [0.79, 1.00]	0.98 [0.96, 1.00]
Boehme 2010c	15	0	1	126	0.94 [0.70, 1.00]	1.00 [0.97, 1.00]
Boehme 2010d	3	0	0	38	1.00 [0.29, 1.00]	1.00 [0.91, 1.00]
Boehme 2010e	119	3	2	61	0.98 [0.94, 1.00]	0.95 [0.87, 0.99]
Boehme 2011a	47	1	3	160	0.94 [0.83, 0.99]	0.99 [0.97, 1.00]
Boehme 2011b	22	1	1	161	0.96 [0.78, 1.00]	0.99 [0.97, 1.00]
Boehme 2011c	9	3	1	175	0.90 [0.55, 1.00]	0.98 [0.95, 1.00]
Boehme 2011d	1	1	2	112	0.33 [0.01, 0.91]	0.99 [0.95, 1.00]
Boehme 2011e	8	2	2	91	0.80 [0.44, 0.97]	0.98 [0.92, 1.00]
Boehme 2011f	149	6	5	97	0.97 [0.93, 0.99]	0.94 [0.88, 0.98]
Bowles 2011	8	0	0	56	1.00 [0.63, 1.00]	1.00 [0.94, 1.00]



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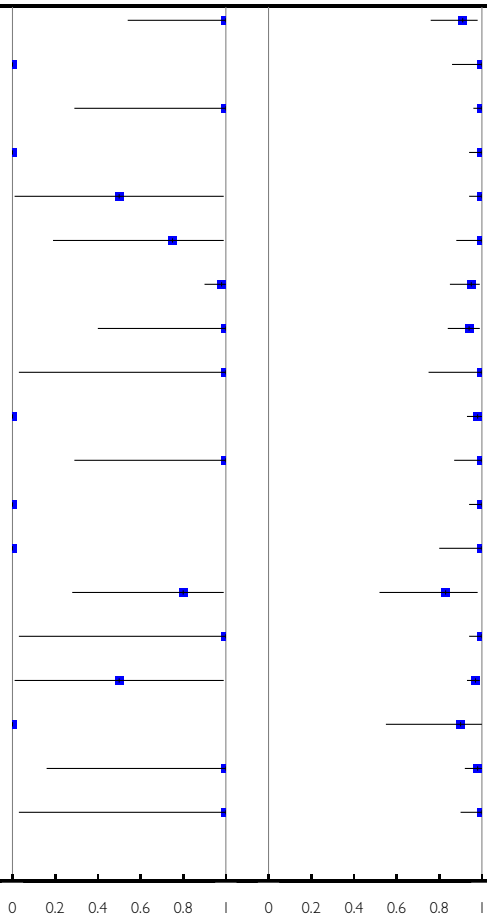
Study	TP	FP	FN	TN	Sensitivity	Specificity
Carriquiry 2012	6	3	0	30	1.00 [0.54, 1.00]	0.91 [0.76, 0.98]
Ciftci 2011	0	0	0	25	0.0 [0.0, 0.0]	1.00 [0.86, 1.00]
Friedrich 2011	3	0	0	90	1.00 [0.29, 1.00]	1.00 [0.96, 1.00]
Hanif 2011	0	0	0	60	0.0 [0.0, 0.0]	1.00 [0.94, 1.00]
Hanrahan 2013	1	0	1	62	0.50 [0.01, 0.99]	1.00 [0.94, 1.00]
Ioannidis 2011	3	0	1	28	0.75 [0.19, 0.99]	1.00 [0.88, 1.00]
Kurbatova 2013	55	2	1	42	0.98 [0.90, 1.00]	0.95 [0.85, 0.99]
Lawn 2011	4	3	0	48	1.00 [0.40, 1.00]	0.94 [0.84, 0.99]
Malbruny 2011	1	0	0	13	1.00 [0.03, 1.00]	1.00 [0.75, 1.00]
Marlowe 2011	0	3	0	127	0.0 [0.0, 0.0]	0.98 [0.93, 1.00]
Miller 2011	3	0	0	26	1.00 [0.29, 1.00]	1.00 [0.87, 1.00]
Rachow 2011	0	0	0	59	0.0 [0.0, 0.0]	1.00 [0.94, 1.00]
Safianowska 2012	0	0	0	17	0.0 [0.0, 0.0]	1.00 [0.80, 1.00]
Scott 2011	4	2	1	10	0.80 [0.28, 0.99]	0.83 [0.52, 0.98]
Teo 2011	1	0	0	61	1.00 [0.03, 1.00]	1.00 [0.94, 1.00]
Theron 2011	1	5	1	151	0.50 [0.01, 0.99]	0.97 [0.93, 0.99]
Van Rie 2013	0	1	0	9	0.0 [0.0, 0.0]	0.90 [0.55, 1.00]
Williamson 2012	2	1	0	64	1.00 [0.16, 1.00]	0.98 [0.92, 1.00]
Zeka 2011	1	0	0	34	1.00 [0.03, 1.00]	1.00 [0.90, 1.00]

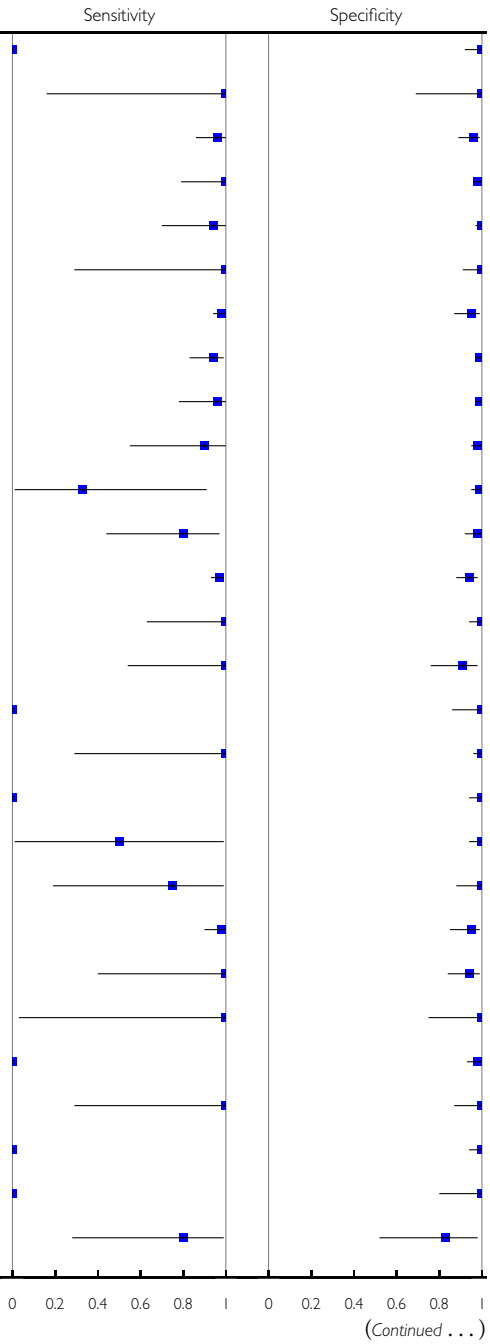


Test 13. Proportion RIF resistance.

Review: Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults

Test: 13 Proportion RIF resistance

Study	TP	FP	FN	TN	Sensitivity	Specificity
Al-Ateah 2012	0	0	0	44	0.0 [0.0, 0.0]	1.00 [0.92, 1.00]
Balcells 2012	2	0	0	10	1.00 [0.16, 1.00]	1.00 [0.69, 1.00]
Boehme 2010a	47	4	2	90	0.96 [0.86, 1.00]	0.96 [0.89, 0.99]
Boehme 2010b	16	3	0	190	1.00 [0.79, 1.00]	0.98 [0.96, 1.00]
Boehme 2010c	15	0	1	126	0.94 [0.70, 1.00]	1.00 [0.97, 1.00]
Boehme 2010d	3	0	0	38	1.00 [0.29, 1.00]	1.00 [0.91, 1.00]
Boehme 2010e	119	3	2	61	0.98 [0.94, 1.00]	0.95 [0.87, 0.99]
Boehme 2011a	47	1	3	160	0.94 [0.83, 0.99]	0.99 [0.97, 1.00]
Boehme 2011b	22	1	1	161	0.96 [0.78, 1.00]	0.99 [0.97, 1.00]
Boehme 2011c	9	3	1	175	0.90 [0.55, 1.00]	0.98 [0.95, 1.00]
Boehme 2011d	1	1	2	112	0.33 [0.01, 0.91]	0.99 [0.95, 1.00]
Boehme 2011e	8	2	2	91	0.80 [0.44, 0.97]	0.98 [0.92, 1.00]
Boehme 2011f	149	6	5	97	0.97 [0.93, 0.99]	0.94 [0.88, 0.98]
Bowles 2011	8	0	0	56	1.00 [0.63, 1.00]	1.00 [0.94, 1.00]
Carriquiry 2012	6	3	0	30	1.00 [0.54, 1.00]	0.91 [0.76, 0.98]
Ciftci 2011	0	0	0	25	0.0 [0.0, 0.0]	1.00 [0.86, 1.00]
Friedrich 2011	3	0	0	90	1.00 [0.29, 1.00]	1.00 [0.96, 1.00]
Hanif 2011	0	0	0	60	0.0 [0.0, 0.0]	1.00 [0.94, 1.00]
Hanrahan 2013	1	0	1	62	0.50 [0.01, 0.99]	1.00 [0.94, 1.00]
Ioannidis 2011	3	0	1	28	0.75 [0.19, 0.99]	1.00 [0.88, 1.00]
Kurbatova 2013	55	2	1	42	0.98 [0.90, 1.00]	0.95 [0.85, 0.99]
Lawn 2011	4	3	0	48	1.00 [0.40, 1.00]	0.94 [0.84, 0.99]
Malbruny 2011	1	0	0	13	1.00 [0.03, 1.00]	1.00 [0.75, 1.00]
Marlowe 2011	0	3	0	127	0.0 [0.0, 0.0]	0.98 [0.93, 1.00]
Miller 2011	3	0	0	26	1.00 [0.29, 1.00]	1.00 [0.87, 1.00]
Rachow 2011	0	0	0	59	0.0 [0.0, 0.0]	1.00 [0.94, 1.00]
Safianowska 2012	0	0	0	17	0.0 [0.0, 0.0]	1.00 [0.80, 1.00]
Scott 2011	4	2	1	10	0.80 [0.28, 0.99]	0.83 [0.52, 0.98]



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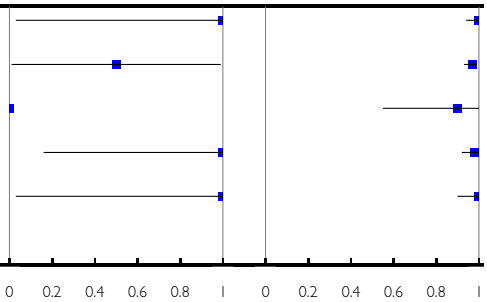
Study	TP	FP	FN	TN	Sensitivity	Specificity
Teo 2011	1	0	0	61	1.00 [0.03, 1.00]	1.00 [0.94, 1.00]
Theron 2011	1	5	1	151	0.50 [0.01, 0.99]	0.97 [0.93, 0.99]
Van Rie 2013	0	1	0	9	0.0 [0.0, 0.0]	0.90 [0.55, 1.00]
Williamson 2012	2	1	0	64	1.00 [0.16, 1.00]	0.98 [0.92, 1.00]
Zeka 2011	1	0	0	34	1.00 [0.03, 1.00]	1.00 [0.90, 1.00]



ADDITIONAL TABLES

Table 1. Xpert MTB/RIF assay for detection of TB and rifampicin resistance

Type of analysis (Number of studies, participants)	Median pooledsensitivity (95% credible interval)	Median pooledspecificity (95% credible interval)	Median predicted sensitivity (95% credible interval)	Median predicted specificity (95% credible interval)
Xpert MTB/RIF used as an initial test for TB detection replacing microscopy (22, 8998)	89% (85, 92)	99% (98, 99)	89% (63, 97)	99% (90, 100)
Xpert MTB/RIF used as an add-on test for TB detection following a negative smear microscopy result (21, 6950)	67% (60, 74)	99% (98, 99)	67% (42, 85)	99% (89, 100)
Xpert MTB/RIF used as an initial test for rifampicin resistance detection replacing conventional DST as the initial test *	95% (90, 97)	98% (97, 99)	95% (80, 99)	98% (94, 100)

* For rifampicin resistance detection, pooled sensitivity and specificity estimates were determined separately by univariate analyses. Pooled sensitivity, number of studies = 17 (555 participants); pooled specificity, number of studies = 24 (2411 participants).

Table 2. Impact of covariates on heterogeneity of Xpert MTB/RIF sensitivity and specificity, TB detection

Covariate (Number of studies)		Median pooled sensitivity (95% credible interval)	Median pooled specificity (95% credible interval)
Smear status			
Smear + (21)		98% (97, 99)	***
Smear - (21)		67% (60, 74)	99% (98, 99)
Difference (Smear+ minus Smear-)		31% (24, 38)	***
P (Smear+ > Smear-)		1.00	***
HIV status			
HIV- (7)		86% (76, 92)	99% (98, 100)
HIV+ (7)		79% (70, 86)	98% (96, 99)
Difference (HIV- minus HIV+)		7% (-5, 18)	1% (-1, 3)
P (HIV- > HIV+)		0.90	0.85
Covariate (number of studies)	**Within smear positive**	**Within smear negative**	
	Median pooled sensitivity (95% credible interval)	**Median pooled sensitivity (95% credible interval)**	**Median pooled specificity (95% credible interval)**
HIV status			
HIV-	***	***	***
HIV+ (4)	97% (90, 99)**	61% (40, 81)**	99% (97, 100)#
Difference (HIV- minus HIV+)	***	***	***
P (HIV- > HIV+)	***	***	***
Condition of specimen			
Fresh (12)	99% (98, 100)	67% (58, 76)	99% (98, 100)
Frozen (6)	97% (95, 99)	61% (48, 73)	98% (95, 99)
Difference (Fresh minus Frozen)	1% (-0.4, 4)	6% (-9, 22)	1% (-0.4, 4)

Table 2. Impact of covariates on heterogeneity of Xpert MTB/RIF sensitivity and specificity, TB detection (*Continued*)

P (Fresh > Frozen)	0.92	0.79	0.92
Specimen preparation			
Unprocessed (10)	98% (97, 99)	69% (60, 78)	98% (97, 99)
Processed (11)	99% (97, 99)	64% (54, 75)	99% (98, 100)
Difference (Unprocessed minus Processed)	-0.1% (-2, 2)	5% (-9, 18)	-1% (-2, 1)
P (Unprocessed > Processed)	0.45	0.76	0.20
Proportion TB cases in the study			
> 30% (12)*	99% (97, 99)	70% (62, 78)	98% (96, 99)
≤ 30% (9)*	98% (96, 99)	61% (50, 73)	99% (98, 100)
Difference (> 30% minus ≤ 30%)	0.5% (-1, 2)	9% (-5, 22)	-1% (-3, 0.2)
P (> 30% minus ≤ 30%)	0.74	0.90	0.05
Country income level			
High-income (8)	99% (98, 100)	73% (62, 83)	99% (97, 100)
Low-income and middle-income (13)	98% (97, 99)	64% (56, 73)	99% (97, 99)
Difference (High-income minus Low- and middle-income)	1% (-1, 2)	9% (-5, 22)	0.3% (-1, 2)
P (High-income > Low- and middle-income)	0.88	0.90	0.69

* We selected 30% as a cut-off based on the median proportion of TB cases in the included studies

**Results are from a univariate analysis

***Values could not be determined

#Results are from a univariate analysis based on three studies

Table 3. Impact of covariates on heterogeneity of Xpert MTB/RIF sensitivity and specificity, rifampicin resistance detection

Covariate	Median pooled sensitivity (95% credible interval)	Median pooled specificity (95% credible interval)
Xpert MTB/RIF assay version*		
G2, G3, G4	93% (87, 97)	98% (96, 99)
G1	97% (91, 99)	99% (98, 100)
Difference (G2, G3, G4 minus G1)	-4% (-10, 3)	-1% (-3, -0.2)
P (G2, G3, G4 > G1)	0.09	0.01
Proportion rifampicin resistance in the study**		
> 15%	96% (91, 98)	97% (94, 99)
≤ 15%	91% (79, 97)	99% (98, 99)
Difference (> 15% minus ≤ 15%)	4% (-3, 16)	-2% (-4, 0.1)
P (> 15% greater than ≤ 15%)	0.87	0.03

Pooled sensitivity and specificity estimates were determined separately by univariate analyses.
*Xpert MTB/RIF assay version G2, G3, G4: pooled sensitivity (13 studies) and pooled specificity (16 studies); Xpert MTB/RIF assay version G1: pooled sensitivity (four studies) and pooled specificity (seven studies).
** Proportion rifampicin resistance > 15%: pooled sensitivity (six studies) and pooled specificity (six studies); proportion rifampicin resistance ≤ 15%: pooled sensitivity (11 studies) and pooled specificity (18 studies).

Table 4. Sensitivity analyses

Type of analysis (Number of studies, participants)	Median pooled sensitivity (95% credible interval)	Median pooled specificity (95% credible interval)	Median predicted sensitivity (95% credible interval)	Median predicted specificity (95% credible interval)
TB detection, without Boehme 2010 and Boehme 2011 (20, 3748)	88% (83, 92)	98% (97, 99)	88% (62, 97)	98% (89, 100)
TB detection, studies that provided data by age that met the criterion for adults (14, 7880)	87% (81, 92)	99% (98, 99)	87% (58, 97)	99% (95, 100)

Table 4. Sensitivity analyses (*Continued*)

TB detection, studies where consecutive patients were selected (17, 8465)	87% (82, 91)	99% (98, 99)	87% (59, 97)	99% (90, 100)
TB detection, studies where a single specimen yielded a single Xpert MTB/RIF result for a given patient (14, 7912)	85% (79, 91)	99% (98, 99)	85% (54, 97)	99% (95, 100)
TB detection, studies that clearly represented the use of the test for diagnosis of patients with presumed TB (16, 7974)	89% (85, 93)	99% (97, 99)	89% (69, 97)	99% (89, 100)
Rifampicin resistance detection by bivariate analyses (17, 2621)	95% (90, 97)	98% (97, 99)	95% (80, 99)	98% (93, 100)

Table 5. Selected patient-important outcomes as reported in the included studies

Study	Time to TB detection	Time to rifampicin resistance detection	Time to treatment initiation
Balcells 2012	Median (range) Xpert MTB/RIF: 0 days Liquid culture 10 days (5 to 22 days) 8 days for smear-positive, 15 days for smear-negative cases		
Boehme 2011	Median (IQR) Xpert MTB/RIF: 0 days (0, 1) Smear: 1 day (0, 1) Solid culture: 30 days (23, 43) Liquid culture: 16 days (13, 21)	Median (IQR) Xpert MTB/RIF: 1 day (0, 1) Line probe assay (direct testing): 20 days (10, 16) Phenotypic DST: 106 days (30, 124)	Median (IQR) Smear-, culture+ TB Before Xpert MTB/RIF introduced: 56 days (39, 81) After Xpert MTB/RIF introduced: 5 days (2, 8)
Helb 2010	Xpert MTB/RIF (1 sample): 1 hour 55 minutes Xpert MTB/RIF (8 samples processed together): 2 hours		
Lawn 2011	Median* (IQR) Xpert MTB/RIF: 4 days (3, 6)	Xpert MTB/RIF: mean 2 days MTBDRplus assay (with positive	

Table 5. Selected patient-important outcomes as reported in the included studies (*Continued*)

	Smear: 3 days (2, 5) Liquid culture (smear+): 12 days (10, 14) Liquid culture (smear-): 20 days (17, 27)	culture isolate): mean 21 days Phenotypic DST (liquid culture): mean 40 days	
Marlowe 2011	Xpert MTB/RIF: hands-on time was 5 minutes; run time was less than 2 hours		
Miller 2011	Xpert MTB/RIF: hands-on time was 15 minutes: run time was 113 minutes		
Moure 2011	Xpert MTB/RIF: total time of 2 hours		
Rachow 2011	Xpert MTB/RIF: within two hours		
Van Rie 2013	Xpert MTB/RIF: results were available the same day		Xpert MTB/RIF positive patients: 0 days (0,0) Patients diagnosed by other methods: 13 days (10, 20)
Zeka 2011**	Xpert MTB/RIF (routine practice): 3 to 24 hours Liquid culture: 19 days mean (range 3 to 42 days)		

*Median delay between sputum collection and results being available to the clinic.
**Times provided for both pulmonary and extrapulmonary specimens jointly.
Abbreviations: DST, drug susceptibility testing; IQR, interquartile range.

APPENDICES

Appendix 1. Detailed search strategies

Search strategy: Medline (OVID) and Embase (OVID)
1. (tuberculosis or TB).tw
limit 1 to yr="2007 -Current"
2. Mycobacterium tuberculosis/
limit 2 to yr="2007 -Current"
3. Tuberculosis, Multidrug-Resistant/ or Tuberculosis/ or Tuberculosis, Pulmonary/
limit 3 to yr="2007 -Current"
4. 1 or 2 or 3
5. (Xpert or GeneXpert or cepheid or(near* patient)). tw.
limit 4 to yr="2007 -Current"
4 and 5
Search strategy: Web of Knowledge (SCI-expanded, SSCI, Conference Proceedings science, BIOSIS previews)
(tuberculosis OR TB OR mycobacterium) (topic) AND (Xpert OR Genexpert OR cepheid) (topic)
Search strategy: LILACS
(tuberculosis OR TB OR mycobacterium) (Words) AND (xpert OR Genexpert OR Cepheid) (Words)
Search strategy: SCOPUS
(tuberculosis OR TB OR mycobacterium) (title, abstract, keywords) AND (xpert OR Genexpert OR Cepheid) (title, abstract, keywords)

Appendix 2. Data extraction form

ID	
ID substudy (for study centres: a, b, c, etc)	
First author	
Corresponding author and email address	
Was author contacted?	1 - Yes 2 - No If yes, dates(s)
Title	
Year (of publication)	
Year (study start date)	
Language	1 - English 2 - Other If other, specify:
For TB detection, what reference standard(s) was used?	1 - Solid culture (specify 1a) 2 - Liquid culture (specify 2a) 3 - Both solid and liquid culture (specify 1a and 2a)

(*Continued*)

	9 - Unknown/not reported 1a - Solid culture LJ 7H10 7H11 Other 2a - Liquid culture MGIT 960 Bactec 460 Other
For rifampicin resistance detection, what reference standard (s) was used?	1 - Solid culture (specify 1a) 2 - Liquid culture (specify 2a) 3 - Both solid and liquid culture (specify 1a and 2a) 9 - Unknown/not reported 1a - Solid culture LJ 7H10 7H11 Other Specify method, for example, proportion Critical concentration for RIF per WHO? 2a - Liquid culture MGIT 960 Bactec 460 Other
Clinical setting; describe as written in the paper	1 - Outpatient 2 - Inpatient 3 - Both out- and in-patient 4 - Other, specify 5 - Laboratory 9 - Unknown/not reported Describe as in paper:
Laboratory services level State name of laboratory	1 - Central 2 - Intermediate 3 - Peripheral 4 - Other, specify
Was Xpert run outside a laboratory, for example, clinic? Describe	1 - Yes 2 - No
Indicate the purpose of testing as described in the study	
Country where study was conducted	
Country World Bank Classification	1 - Middle/low 2 - High

(*Continued*)

	3 - Both middle/low and high
Study design	1 - RCT 2 - Cross-sectional 3 - Cohort 4 - Other, specify 9 - Unknown/not reported If other, specify:
Participant selection	1 - Consecutive 2 - Random 3 - Convenience 7 - Other 9 - Unknown/not reported
Direction of study data collection	1 - Prospective 2 - Retrospective 9 - Unknown/not reported
Number after screening by inclusion and exclusion criteria	____ 9 - Unknown/not reported
Number included in analysis (# screened - # withdrawals)	____ 9 - Unknown/not reported
Unit of analysis	1 - One specimen per patient 2 - Multiple specimens per patient 3 - Unknown number of specimens per patient 9 - Unknown/not reported Describe as in paper, if unclear:
Prior testing by microscopy	1 - Yes 2 - No 9 - Unknown/not reported
Was the index test result interpreted without knowledge of the result of the reference standard result?	1 - Yes
TB detection: Was the reference standard result interpreted without knowledge of the index test result of the result?	1 - Yes 2 - No 9 - Unknown/not reported
Rifampicin resistance detection: Was the reference standard result interpreted without knowledge of the index test result of the result?	1 - Yes 2 - No 9 - Unknown/not reported
Comments about study design	

(*Continued*)

Patient characteristics and setting	
Age (range, mean (SD), median (IQR)	
% female	
Did the study include patients with previous TB history?	1 - Yes 2 - No 9 - Unknown/not reported
If so, what is the percentage?	% Specify numerator/denominator
HIV status of participants	0 - HIV - 1 - HIV + 2 - Both HIV+/- 9 - Unknown/not reported
If HIV-positive participants included, what is the percentage?	% Specify numerator/denominator
Type of specimen (may include expectorated, induced, bronchial alveolar lavage (BAL), tracheal aspirates)	1 - All expectorated 2 - All induced 3 - All BAL 4 - Multiple types 5 - Other 9 - Unknown/not reported If 4 or 5, describe types and record numbers:
Were Xpert sample and culture obtained from same specimen?	1 - Yes 2 - No 9 - Unknown/not reported
Number of cultures used to exclude TB	1 - One 2 - Two 3 - Three 4 - Four 5 - Other, specify 9 - Unknown/not reported Specify, if > 4: NOTES:
Pre-treatment processing procedure for Xpert	1 - None 2 - NALC-NaOH 3 - NaOH (Petroff) 4 - Other 9 - Unknown/not reported

(*Continued*)

Was microscopy used	1 - Yes 2 - No 9 - Unknown/not reported
Type of microscopy used	1 - Ziehl-Neelsen 2 - FM 9 - Unknown/not reported
Smear type	1 - Direct 2 - Concentrated (processed) 9 - Unknown/not reported
Minimum number of sputum specimens used to determine smear positivity	1 - One 2 - Two 3 - Three 4 - > 3 9 - Unknown/not reported
How was a positive smear defined? (if guideline referenced, look up guideline)	≥___bacilli per___ high power fields 9 - Unknown/not reported * Complete both fields
For Xpert specimen, what was the condition of the specimen when tested?	1 - Fresh 2 - Frozen 9 - Unknown/not reported
If fresh, specify:	1 - Tested after storage at room temperature or if refrigerated within 48 hours of collection 2 - Tested after storage at room temperature or if refrigerated > 48 hours after collection 9 - Unknown/not reported
If frozen, specify:	1 - Tested after frozen < 1 year of storage 2 - Tested frozen ≥ 1 year of storage 9 - Unknown/not reported
Version of software for test interpretation	1 - Version 1 2 - Version 2 3 - Version 3 4 - Version 4 9 - Unknown/not reported
Enter percentage contaminated cultures, if provided: **Number contaminated culture results/ Total number cultures performed**	_____ 9 - Unknown/not reported

(*Continued*)

Were uninterpretable results reported for Xpert for TB detection?	1 - Yes 2 - No 9 - Unknown/not reported
Were uninterpretable results reported for Xpert for rifampicin resistance detection?	1 - Yes 2 - No 9 - Unknown/not reported
Were patient important outcomes evaluated?	1 - Yes 2 - No 9 - Unknown/not reported
Time to diagnosis	Xpert: Culture: 9 - Unknown/not reported
Time to treatment initiation	Xpert: Culture: 9 - Unknown/not reported
Other patient outcomes	Specify:
Number NTM/Number of specimens tested; provide Xpert results	

TABLES

TB detection, all studies		**Confirmed TB**		
		Yes	**No**	**Total**
Xpert result	Positive			
	Negative			
	Total			
	Uninterpretable			

TB detection, smear positive		Confirmed TB		
		Yes	No	Total
Xpert result	Positive			
	Negative			
	Total			
	Uninterpretable			

TB detection, smear negative		Confirmed TB		
		Yes	No	Total
Xpert result	Positive			
	Negative			
	Total			
	Uninterpretable			

TB detection, HIV-positive		Confirmed TB		
		Yes	No	Total
Xpert result	Positive			
	Negative			
	Total			
	Uninterpretable			

TB detection, HIV-negative		Confirmed TB		
		Yes	No	Total
Xpert result	Positive			
	Negative			

(*Continued*)

	Total			
	Uninterpretable			

RIF resistance detection		**Confirmed rifampicin resistance**		
		Yes	**No**	**Total**
Xpert result	Yes (resistant)			
	No (susceptible)			
	Total			
	Uninterpretable			

Smear microscopy		**Confirmed TB**		
		Yes	**No**	**Total**
Smear result	Positive			
	Negative			
	Total			

Appendix 3. Rules for QUADAS-2

Domain 1: Patient selection

Risk of bias: Could the selection of patients have introduced bias?

Signalling question 1: Was a consecutive or random sample of patients enrolled? We scored 'yes' if the study enrolled a consecutive or random sample of eligible patients; 'no' if the study selected patients by convenience; and 'unclear' if the study did not report the manner of patient selection or we could not tell.

Signalling question 2: Was a case-control design avoided? Studies using a case-control design were not included in the review because this study design, especially when used to compare results in severely ill patients with those in relatively healthy individuals, may lead to overestimation of accuracy in diagnostic studies. We scored 'yes' for all studies.

Signalling question 3: Did the study avoid inappropriate exclusions? We scored 'yes' if the study included both smear-positive and smear-negative individuals or only smear-negative individuals; 'no' if the study included only smear-positive individuals; and 'unclear' if we could not tell.

Applicability: Are there concerns that the included patients and setting do not match the review question?

We were interested in how Xpert MTB/RIF performed in patients presumed to have pulmonary TB or MDR-TB whose specimens (predominantly sputum specimens) were evaluated as they would be in routine practice, in intermediate-level laboratories or primary health care facilities. We judged 'unclear' concern if Xpert MTB/RIF was run in a central-level laboratory. We assumed a central-level

laboratory used highly trained staff. However, we acknowledge, that for some studies, the reason Xpert MTB/RIF was performed in the central-level laboratory was the requirement for a sophisticated laboratory infrastructure to perform culture (the reference standard) not to perform Xpert MTB/RIF. We judged 'high concern' if the majority of specimens were respiratory specimens other than sputum.

Domain 2: Index test

Risk of bias: Could the conduct or interpretation of the index test have introduced bias?
Signalling*question 1: Were the index test results interpreted without knowledge of the results of the reference standard?* We answered this question 'yes' for all studies because Xpert test results were automatically generated and the user was provided with printable test results. Thus, there is no room for subjective interpretation of test results.
Signalling*question 2: If a threshold was used, was it prespecified?* The threshold was prespecified in all versions of Xpert. We answered this question 'yes' for all studies.
For risk of bias, we scored 'low concern' for all studies.
Applicability: Are there concerns that the index test, its conduct, or its interpretation differ from the review question? Variations in test technology, execution, or interpretation may affect estimates of the diagnostic accuracy of a test. However, we judged these issues to be of 'low concern' for all studies in this review.

Domain 3: Reference standard

Risk of bias: Could the reference standard, its conduct, or its interpretation have introduced bias?
We considered this domain separately for the reference standard for TB detection and the reference standard for rifampicin resistance.
Signalling*question 1: Is the reference standard likely to correctly classify the target condition?* For pulmonary TB: although culture is not 100% accurate, it is considered to be the gold standard for TB diagnosis. For rifampicin resistance: similarly, although DST by conventional phenotypic methods is not 100% accurate, it is considered to be the gold standard. We answered this question 'yes' for all studies.
Signalling*question 2: (TB) Were the reference standard results interpreted without knowledge of the results of the index test?* We scored 'yes' if the reference test provided an automated result (for example, MGIT 960), blinding was explicitly stated, or it was clear that the reference standard was performed at a separate laboratory and/or performed by different people. We scored 'no' if the study stated that the reference standard result was interpreted with knowledge of the Xpert test result. We scored 'unclear' if we could not tell.
Signalling*question 3: (Rifampicin resistance)* We added a signalling question for rifampicin resistance because judgments might differ for TB and for rifampicin resistance, the two target conditions. *Were the reference standard results interpreted without knowledge of the results of the index test?* We scored 'yes' if the reference test provided an automated result (for example, MGIT 960), blinding was explicitly stated, or it was clear that the reference standard was performed at a separate laboratory and/or performed by different people. We scored 'no' if the study stated that the reference standard result was interpreted with knowledge of the Xpert test result. We scored 'unclear' if we could not tell.
Applicability: Are there concerns that the target condition as defined by the reference standard does not match the question? We judged applicability to be of 'low concern' for all studies for both pulmonary TB and rifampicin resistance.

Domain 4: Flow and timing

Risk of bias: Could the patient flow have introduced bias?
Signalling*question 1: Was there an appropriate interval between the index test and reference standard?* In the majority of included studies, we expected specimens for Xpert and culture to be obtained at the same time when patients were presumed to have TB. However, even if there were a delay of several days or weeks between index test and reference standard, TB is a chronic disease and we considered misclassification of disease status to be unlikely. We answered this question 'yes' for all studies.
Signalling*question 2: Did all patients receive the same reference standard?* We answered this question 'yes' for all studies as an acceptable reference standard (either solid or liquid culture) was specified as a criterion for inclusion in the review. However, we acknowledge that it is possible that some specimens could undergo solid culture and others liquid culture. This could potentially result in variations in accuracy, but we thought the variation would be minimal.
Signalling*question 3: Were all patients included in the analysis?* We determined the answer to this question by comparing the number of patients enrolled with the number of patients included in the two-by-two tables.

Appendix 4. Statistical appendix

Bayesian bivariate hierarchical model

The Bayesian bivariate hierarchical model used for the meta-analyses is summarized below. The hierarchical framework took into account heterogeneity between studies and also between centres within two of the largest studies. The model was derived as an extension of previously described models (Chu 2009; Reitsma 2005). A WinBUGS program to fit this model is provided below. Three independent, dispersed sets of starting values were used to run separate chains. The Gelman-Rubin statistic within the WinBUGS program was used to assess convergence. No convergence problems were observed. The first 3000 iterations were treated as burn-in iterations and dropped. Summary statistics were obtained based on a total of 15,000 iterations resulting from the three separate chains.

Notation: From the j^{th} centre in the i^{th} study we extracted the cross-tabulation between the index and reference tests TP_{ij}, FP_{ij}, TN_{ij}, FN_{ij}. The sensitivity in ij^{th} study is denoted by S_{ij} and the specificity by SP_{ij}. We denote the Binomial probability distribution with sample size N and probability p as Binomial(p,N), the Bivariate Normal probability distribution with mean vector μ and variance-covariance matrix Σ as BVN(μ, Σ), the univariate Normal distribution with mean m and variance s by N(m, s) and the Uniform probability distribution between a and b by Uniform(a,b).

Likelihood Figure 13:

Figure 13. Bayesian bivariate hierarchical model, likelihood.

Centre-level:

For studies with only 1 centre:

$$TP_{i1} \sim Binomial(S_i, TP_{i1} + FN_{i1}), TN_{i1} \sim Binomial(SP_i, TN_{i1} + FP_{i1})$$

For multicentre studies:

$$TP_{ij} \sim Binomial(S_{ij}, TP_{ij} + FN_{ij}), TN_{ij} \sim Binomial(SP_{ij}, TN_{ij} + FP_{ij})$$

$$\begin{pmatrix} logit(S_{ij}) \\ logit(SP_{ij}) \end{pmatrix} \sim BVN(l_i, \Sigma_i),$$

where $l_i = \begin{pmatrix} logit(S_i) \\ logit(SP_i) \end{pmatrix}$ and $\Sigma_i = \begin{pmatrix} \sigma_{i1}^2 & k_i\sigma_{i1}\sigma_{i2} \\ k_i\sigma_{i1}\sigma_{i2} & \sigma_{i2}^2 \end{pmatrix}$

Study-level:

$$\begin{pmatrix} logit(S_i) \\ logit(SP_i) \end{pmatrix} \sim BVN\left(\mu = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, T = \begin{pmatrix} \tau_1^2 & \rho\tau_1\tau_2 \\ \rho\tau_1\tau_2 & \tau_2^2 \end{pmatrix}\right)$$

The pooled sensitivity is given by 1/1+exp (-μ_1) and pooled specificity as 1/1+exp (μ_2).
Prior distributions Figure 14:

Figure 14. Bayesian bivariate hierarchical model, prior distributions.

$$\mu_1 \text{ and } \mu_2 \sim N(0, 100)$$

$$k_i \text{ and } \rho \sim U(-1,1)$$

$$\frac{1}{\sigma_1^2}, \frac{1}{\sigma_2^2}, \frac{1}{\tau_1^2} \text{ and } \frac{1}{\tau_2^2} \sim Gamma(\text{shape}=2, \text{rate}=0.5)$$

Meta-regression models:
To examine the impact of a dichotomous covariate (Z) on the pooled sensitivity and specificity parameters, we expressed the logit(sensitivity) and logit(specificity) as linear functions of Z as follows:
$\mu_1 = a_1 + b_1 Z$ and $\mu_2 = a_2 + b_2 Z$
Prior distributions were placed over the coefficients in the linear function: a_1 and $a_2 \sim$ N(0,4) and b_1 and $b_2 \sim$ N(0,1.39) (Buzoianu 2008).

```
-----------------------------------------------------------------------------------------------------------------------------------------------------------
# WinBUGS PROGRAM FOR ESTIMATING A BIVARIATE HIERARCHICAL META-ANALYSIS MODEL
# FOR SENSITIVITY AND SPECIFICITY ALLOWING FOR HETEROGENEITY BETWEEN STUDIES
# AND HETEROGENEITY BETWEEN CENTRES WITHIN TWO OF THE STUDIES (BOEHME 2010 and 2011)
 model {
 ##############################    BOEHME 2010    ##############################
            for(j in 1:5) {

                        logit(se.q[j])<-q1[j,1]
                        logit(sp.q[j])<-q1[j,2]

                        q1[j,1:2]~ dmnorm(l[1,1:2], T1[1:2,1:2])

                        pos1[j]<-TP1[j]+FN1[j]
                        neg1[j]<-TN1[j]+FP1[j]
                        TP1[j] ~ dbin(se.q[j],pos1[j])
                        FP1[j] ~ dbin(sp.q[j],neg1[j])
            }
             T1[1:2,1:2]<-inverse(SIGMA1[1:2,1:2])

            # Between-centre variance-covariance matrix for Boehme 2010
            SIGMA1[1,1] <- sigma1[1]*sigma1[1]
            SIGMA1[2,2] <- sigma1[2]*sigma1[2]
```

```
        SIGMA1[1,2] <- k1*sigma1[1]*sigma1[2]
        SIGMA1[2,1] <- k1*sigma1[1]*sigma1[2]

        prec1[1] ~ dgamma(2,0.5)
        prec1[2] ~ dgamma(2,0.5)
        k1 ~ dunif(-1,1)
        sigma1[1]<-pow(prec1[1],-0.5)
        sigma1[2]<-pow(prec1[2],-0.5)

        # Overall sens/spec across centres in Boehme 2010
        se[1]<-1/(1+exp(-l[1,1]))
        sp[1]<-1/(1+exp(l[1,2]))

        l[1,1:2] ~ dmnorm(mu[1:2], T[1:2,1:2])

############################    BOEHME 2011    ############################
         for(j in 1:6) {

                logit(se.r[j])<- r1[j,1]
                logit(sp.r[j])<- r1[j,2]

                r1[j,1:2]~ dmnorm(l[2,1:2], T2[1:2,1:2])

                pos2[j]<-TP2[j]+FN2[j]
                neg2[j]<-TN2[j]+FP2[j]
                TP2[j] ~ dbin(se.r[j],pos2[j])
                FP2[j] ~ dbin(sp.r[j],neg2[j])

        }
         T2[1:2,1:2]<-inverse(SIGMA2[1:2,1:2])

        # Between-centre variance-covariance matrix for Boehme 2011
        SIGMA2[1,1] <- sigma2[1]*sigma2[1]
        SIGMA2[2,2] <- sigma2[2]*sigma2[2]
        SIGMA2[1,2] <- k2*sigma2[1]*sigma2[2]
        SIGMA2[2,1] <- k2*sigma2[1]*sigma2[2]

        prec2[1] ~ dgamma(2,0.5)
        prec2[2] ~ dgamma(2,0.5)
        k2 ~ dunif(-1,1)
        sigma2[1]<-pow(prec2[1],-0.5)
        sigma2[2]<-pow(prec2[2],-0.5)

        # Overall sens/spec across centres in Boheme 2011
        se[2]<-1/(1+exp(-l[2,1]))
        sp[2]<-1/(1+exp(l[2,2]))

        l[2,1:2] ~ dmnorm(mu[1:2], T[1:2,1:2])

############################    SINGLE CENTRE STUDIES    ############################
         for(i in 3:22) {

                logit(se[i]) <- l[i,1]
```

```
                logit(sp[i]) <- l[i,2]

                pos[i]<-TP[i]+FN[i]
                neg[i]<-TN[i]+FP[i]
                TP[i] ~ dbin(se[i],pos[i])
                FP[i] ~ dbin(sp[i],neg[i])

                l[i,1:2] ~ dmnorm(mu[1:2], T[1:2,1:2])
        }
 ############################    HYPER PRIOR DISTRIBUTIONS    ############################

        mu[1] ~ dnorm(0,0.25)
        mu[2] ~ dnorm(0,0.25)

        T[1:2,1:2]<-inverse(TAU[1:2,1:2])

        # Between-study variance-covariance matrix
        TAU[1,1] <- tau[1]*tau[1]
        TAU[2,2] <- tau[2]*tau[2]
        TAU[1,2] <- rho*tau[1]*tau[2]
        TAU[2,1] <- rho*tau[1]*tau[2]

        tau[1]<-pow(prec[1],-0.5)
        tau[2]<-pow(prec[2],-0.5)

        # prec is the between-study precision in the logit(sensitivity) and logit(specificity)
        prec[1] ~ dgamma(2,0.5)
        prec[2] ~ dgamma(2,0.5)
        rho ~ dunif(-1,1)

        # Pooled sensitivity and specificity
        Pooled.S<-1/(1+exp(-mu[1]))
        Pooled.C<-1/(1+exp(mu[2]))

        # Predicted sensitivity and specificity in a new study
        l.new[1:2] ~ dmnorm(mu[],T[,])
        sens.new <- 1/(1+exp(-l.new[1]))
        spec.new <- 1/(1+exp(l.new[2]))

}
 ############################## DATA ###################################
 # DATA WAS READ FROM THREE SEPARATE FILES

# DATA 1 - BOEHME 2010
TP1[]    FP1[]    FN1[]    TN1[]
123      1        24       68
201      0        8        101
136      1        10       185
36       3        7        215
179      0        8        35
END

#row 1 : Azerbaijan
```

#row 2 : Peru
#row 3 : South Africa, Cape Town
#row 4 : South Africa, Durban
#row 5 : India
##
DATA 2 - FROM BOEHME 2011
TP2[] FP2[] FN2[] TN2[]
203 4 26 303
171 3 6 825
201 2 32 669
121 0 24 144
101 16 0 671
136 5 12 234
END

#Boheme 2011
#row 1 : Azerbaijan
#row 2 : Peru
#row 3 : South Africa
#row 4 : Uganda
#row 5 : India
#row 6 : The Philippines
##
DATA 3 - FROM BOEHME 2011

TP[] FP[] FN[] TN[]
NA NA NA NA
NA NA NA NA
42 0 2 128
11 1 1 147
37 0 15 16
60 1 4 29
44 2 1 84
24 1 1 59
54 0 6 146
41 2 22 479
67 0 15 25
102 17 5 104
42 2 30 320
12 0 0 46
116 4 14 82
27 2 2 58
61 1 8 102
15 1 2 127
58 3 9 107
56 2 6 55
111 19 30 320
31 0 4 68
END

#row 1 : Boheme 2010
#row 2 : Boheme 2011
#row 3 : Al-Ateah 2012

#row 4 : Balcells 2012
#row 5 : Barnard 2012
#row 6 : Bowles 2011
#row 7 : Carriquiry 2012
#row 8 : Cifci 2011
#row 9 : Hanif 2011
#row 10 : Hanrahan 2013
#row 11 : Helb 2010
#row 12 : Kurbatova 2012
#row 13 : Lawn 2011
#row 14 : Malbruny 2011
#row 15 : Marlowe 2011
#row 16 : Miller 2011
#row 17 : Rachow 2011
#row 18 : Safianowska 2012
#row 19 : Scott 2011
#row 20 : Teo 2011
#row 21 : Theron 2011
#row 22 : Zeka 2011
##

FEEDBACK

Boyles, 7 October 2014

Summary

Name: Tom Boyles
Affiliation: University of Cape Town
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.
In the initial version of Steingart et al's systematic review of the Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults (Steingart 2013) includes 15 studies where Xpert was used as an initial test replacing smear microscopy, with the majority of patients being drawn from two major studies (Boehme 2010a, Boehme 2011a). My comment relates to the appropriate reference standard for tuberculosis is these studies. The systematic review appraised the quality of included studies with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (Whiting 2011) tool which states that estimates of test accuracy are based on the assumption that the reference standard is 100% sensitive and that specific disagreements between the reference standard and index test result from incorrect classification by the index test.
For each of the studies in question the reference standard for tuberculosis is listed as "Löwenstein-Jensen culture and MGIT 960" and the review considers that the reference standard is likely to correctly classify the target condition. There is considered to be low risk of bias or applicability concerns relating to the reference test.
However, in Boehme et al 2010 there were 105 patients with 'clinical tuberculosis' who were excluded from the analysis. These patients were negative by the reference standard of Löwenstein-Jensen culture and MGIT 960 and should have been included in the 'no tuberculosis' group. In Boehme et al 2011 there were 153 similar patients who were excluded from the analysis.
Neither paper gives justification for the exclusion of these patients who according to QUADAS-2 were negative by the reference standard and should be included in the 'no tuberculosis' group. Ideally the systematic review should be amended to include these patients but if the data is unavailable the risk of bias should be acknowledged.
Note from the Editors: In addition to the above feedback, Boyles et al. published a case study in The International Journal of Tuberculosis and Lung Disease which outlined the above arguments, and illustrates this with a case study (Boyles 2014); which the Cochrane authors respond to, in the same journal (see below).

Reply

The review authors thank Boyles et al. for this comment. They raise important points about the selective exclusion of culture negative clinical TB cases in the Boehme studies.

We considered the published case study (Boyles 2014) in detail, and in response we carried out additional analyses to determine whether the Boehme studies unduly influenced the overall findings of this Cochrane review. One way we did this was by repeating the meta-analysis with studies for which we could extract data for all enrolled participants, including patients classified as 'clinical tuberculosis' with negative sputum culture. We considered these participants as not having TB. In the new analysis, we found pooled sensitivity and specificity estimates to be similar to those we previously reported.

We published our findings as a response to Boyles et al. in *The International Journal of Tuberculosis and Lung Disease* (Steingart 2015).

WHAT'S NEW

Date	Event	Description
16 March 2015	Feedback has been incorporated	Feedback from Dr Tom Boyles at University of Cape Town has been incorporated and responded to

HISTORY

Protocol first published: Issue 1, 2012

Review first published: Issue 1, 2013

Date	Event	Description
6 May 2014	Amended	Following information from one of the trial authors, details of the version of Xpert MTB/RIF used in Balcells 2012 have been corrected.
13 February 2014	Amended	Sentence moved in abstract; corrected 'pooled median sensitivity' to 'median pooled sensitivity' throughout
30 November 2013	New search has been performed	1. We performed an updated literature search on 7 February 2013. 2. For smear microscopy as a comparator test, we added a descriptive plot showing the estimates of sensitivity and specificity of Xpert compared with those of smear microscopy in studies that reported on both tests. 3. We included studies using Xpert version G4 (two studies) and studies evaluating Xpert in primary care clinics (two studies). These studies did not change the overall findings. 4. We improved the QUADAS-2 assessment concerning applicability. 5. For TB detection, we repeated our earlier meta-

(*Continued*)

		regression analyses within subgroups defined by smear status. 6. For rifampicin resistance detection, we performed univariate meta-analyses for sensitivity and specificity separately in order to include studies in which no rifampicin resistance was detected. We also performed a sensitivity analysis using the bivariate random-effects model for the subset of studies that provided data for both sensitivity and specificity. 7. We revised the summary of findings table to include clinical scenarios with prevalence levels recommended by the World Health Organization. 8. In the Background, we shortened the section on alternative tests to include only those tests most relevant to the review. 9. We added health economic considerations to the Discussion 10. We added updated TB surveillance information.
30 November 2013	New citation required but conclusions have not changed	We conducted a new search and revised the review as described
17 January 2013	Amended	We made some minor edits to the text to correct typographical errors. In addition, we replaced Figures 6, 8, 11, and 13 with new figures with minor modifications to the prediction regions

CONTRIBUTIONS OF AUTHORS

MP conceived the original idea for the review. KRS, MP, and ND wrote the protocol. LAK drafted the search strategy. For this updated Cochrane Review, KRS and DH reviewed articles for inclusion and extracted data. KRS, IS, and ND analysed the data. KRS, MP, and ND interpreted the analyses. KRS drafted the manuscript. ND drafted the statistical analysis section and Appendix 4. KRS, CCB, MP, and ND provided critical revisions to the manuscript. All authors read and approved the final manuscript draft.

DECLARATIONS OF INTEREST

The CIDG provided funding in part for this review. KRS serves as Co-ordinator of the Evidence Synthesis and Policy Subgroup of Stop TB Partnership's New Diagnostics Working Group. KRS received funding to carry out the original Cochrane Review from CIDG and McGill University and the updated Cochrane Review from the United States Agency for International Development (USAID), USA. MP is a recipient of a New Investigator Award from the Canadian Institutes of Health Research (CIHR) and a salary award from Fonds de recherche du Québec - Santé. MP serves as an external consultant for the Bill & Melinda Gates Foundation. CCB is employed by the Foundation for Innovative New Diagnostics (FIND) and has conducted studies and published on Xpert MTB/RIF as part of a collaborative project between FIND, a Swiss non-profit, Cepheid, a US company, and academic partners. The product developed through this partnership was developed under a contract that obligated FIND to pay for development costs and trial costs and Cepheid to make the test available at specified preferential pricing to the public sector in developing countries. The authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or

materials discussed in the review apart from those disclosed. IS received funding to carry out the updated Cochrane Review from CIDG and USAID.

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- Liverpool School of Tropical Medicine, UK.

External sources

- United States Agency for International Development (USAID), USA.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we stated that we would extract data on industry sponsorship. However, we became aware that the Foundation for Innovative New Diagnostics (FIND) had negotiated a special price for the assay for TB endemic countries. As the majority of the included study centres were located in TB endemic countries, we assumed Xpert MTB/RIF had been purchased at the negotiated price. Therefore, we did not consider the included studies to be sponsored by industry.

We compared the accuracy of Xpert MTB/RIF for TB detection in high-income versus low- and middle-income countries. This comparison was not mentioned in the protocol. NTM were not mentioned in the protocol. In the update, NTM were considered non-TB. We summarized separately data for NTM by determining the percent of false-positive Xpert MTB/RIF results in samples that grew NTM.

We stated we would discuss the consequences when an uninterpretable test result was considered to be a (false) true negative result (may lead to missed/delayed diagnosis, with potential for increased morbidity, mortality, and TB transmission), or considered to be a (false) true positive result (may lead to unnecessary treatment with adverse events and increased anxiety). Since the rate of uninterpretable results was very low, we did not discuss these consequences.

Exploration of different reference standards, culture and clinical, while an interesting and important question, was beyond what we could carryout in an already complex review, with two review questions and multiple factors (including condition of specimen, income status, clinical subgroups) that could affect the summary estimates.

We performed additional sensitivity analyses for studies that did not clearly report the reason for testing and clinical information about patients and for studies that did not explicitly report patient age.

We initially used QUADAS, as mentioned in the protocol, but switched to QUADAS-2 for the original review and updated review.

For smear microscopy as a comparator test, we added a descriptive plot showing the estimates of sensitivity and specificity of Xpert MTB/RIF compared to estimates of sensitivity of smear microscopy in studies that reported on both tests. We assumed smear specificity was 100%.

For TB detection, we repeated our earlier meta-regression analyses within subgroups defined by smear status.

INDEX TERMS

Medical Subject Headings (MeSH)

*Drug Resistance, Bacterial; Antibiotics, Antitubercular [*therapeutic use]; Mycobacterium tuberculosis [*drug effects; genetics; *isolation & purification]; Polymerase Chain Reaction [*methods]; Rifampin [*therapeutic use]; Sensitivity and Specificity; Sequence Analysis, DNA [methods]; Tuberculosis, Pulmonary [diagnosis; *drug therapy]

MeSH check words

Adult; Humans